PRACTICAL NEUROLOGY

FOURTH EDITION

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This book is dedicated to:
My parents Elena and Osías
My wife Rhonda, my children Sofía,
Gabriel, and Rebecca and my stepchildren
Adam and Emily
My grandchildren Selim and Ira
Our patients who entrust their care to us

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SECTION II. Treatment

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Preface to the Fourth Edition

This new edition of *Practical Neurology* is designed to provide a rapid yet comprehensive update on the growing knowledge of neurologic diagnosis and therapeutics. Each of the authors has distilled within its pages a wealth of information, from their experienced vantage point, that summarizes the optimal, most accepted diagnostic and therapeutic consensus. This approach is meant to close the divide between the poorly digested, difficult-to-generalize, evidence-based medicine and the multiplicity of clinical dilemmas where such evidence is weak or absent altogether. In sum, this "real life" guide to neurology is deliberately meant to represent the practical take on advances in the understanding of diseases and treatments by clinicians experienced in the day-to-day treatment of patients with neurologic disorders.

Because it is developed from the learner's standpoint, we hope the format of this new edition again lends itself to being a user friendly and readily accessible guide. The text follows the general outline of the first three editions, and is divided into two parts: (1) 35 chapters on fundamental information on roadmaps to diagnosis, and (2) 23 chapters on treatment—including "ABCs" of neurologic emergencies. The current volume has been completely rewritten to cover advances over the past decade and is intended to pragmatically assist those residents, fellows, and practicing physicians, and thus, positively impact better care for people who live with a variety of neurologic disorders.

My deepest thanks to the contributing authors for their devotion to the task at hand, and their generosity in giving their time and expertise to the preparation of this new edition. Many individuals provided help and support during the writing of this book. I especially thank Tom Gibbons, Frances Destefano, and other members of the design and production team of Wolters Kluwer–Lippincott Williams & Wilkins for their constant encouragement and professionalism; and Linda Turner for her wonderful secretarial and administrative expertise. Finally, I lovingly thank my wife Rhonda for her unfailing humor, encouragement and support.

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SECTION I DIAGNOSIS

CHAPTER 1

Approach to the Patient with Acute Confusional State (Delirium/ Encephalopathy)

John C. Andrefsky and Jeffrey I. Frank

Delirium is a syndrome characterized by confusion with inattention, alteration of arousal, disorientation, and global cognitive impairment. All patients with delirium should be promptly evaluated because of the progressive and potentially lethal nature of many of the etiologic factors as well as the danger these patients may pose to themselves. Management of the underlying cause leads to resolution in most circumstances. In this chapter, the terms *delirium* and *confusion* are used interchangeably.

All physicians encounter delirious patients during their careers, and knowing the patients at risk for delirium improves early recognition of the syndrome. The point prevalence of adults in the general population older than 55 years is 1.1%. About 10% to 40% of the hospitalized elderly and 60% of nursing home patients older than 75 years are delirious. Patients with cancer, AIDS, or a terminal illness and those who have undergone bone marrow transplantation and other surgical procedures are at increased risk of delirium.

I. ETIOLOGY

The common pathophysiologic mechanism of all causes of delirium is widespread dysfunction of both the cortical and the subcortical neurons.

A. The causes can affect a focal population or disrupt neuronal functioning diffusely.

B. The neurotransmitters **acetylcholine** and **dopamine** are known to play a central role in the regulation and communication of large numbers of neurons.

1. Cholinergic neuronal pathways serve almost all areas of the brain and participate in most executive brain functions, including those of a delirious patient.

a. Anticholinergic medications induce hyperactivity and decrease the ability to selectively attend.

2. Dopaminergic neurons are primarily found in the nigrostriatal, hypothalamic-pituitary, and ventral tegmental areas but diffusely project to the frontal and temporal areas responsible for delirious symptoms.

3. Intoxication with dopamine agonists commonly causes delirium.

4. Antidopaminergic (neuroleptics) actions are commonly used to manage delirium.

The causes of delirium (Table 1.1) include commonly encountered and rare conditions. Many are reversible and carry an excellent prognosis if the patient is treated in a timely manner. The following are the basic etiologic categories of delirium.

A. Infection is one of the most common causes of delirium.

1. Systemic infections always should be considered, especially with elderly patients and those with previous brain damage.

2. CNS infections should be a primary consideration in the postoperative neurosurgical and immunosuppressed patients.

B. Metabolic abnormalities are a common cause of delirium and often coexist with other precipitants of delirium.

C. End-organ failure manifests as striking abnormalities at general physical examination and usually is readily recognized.

1. Failure to promptly control hypotension and hypoxia can allow patients to suffer severe brain damage.

2. Liver and kidney failure can cause delirium alone or decrease the metabolism and excretion of certain medications and their metabolites.

TABLE 1.1 Causes of Delirium

Infection

Outside CNS
- Sepsis
- Localized

CNS
- Meningitis
  - Bacterial
  - Tuberculous
  - Cryptococcal
  - Lyme disease
  - Syphilitic
- Toxoplasmosis
- Tertiary syphilis
- Encephalitis
  - Herpes simplex

PML
HIV virus
Abscess
- Brain
- Epidural

Subdural empyema
Subacute spongiform encephalopathy
Whipple's disease

Autoimmune

ADEM
Systemic lupus erythematosus

Metabolic abnormalities

Electrolyte disorders
Hyperosmolality, hypoosmolality
CPM
Hypernatremia, hyponatremia
Hypokalemia
Hypercalcemia
Hypophosphatemia
Hypermagnesemia, hypomagnesemia
Acid–base disorders
- Acidosis
- Alkalosis

End-organ failure

Hyperglycemia
- Diabetic ketoacidosis
- Hyperosmolar nonketotic hyperglycemia

Hypoglycemia
Hypercapnia
Hypoxia
Hypotension
Uremia
Hepatic encephalopathy
Reye's syndrome
Pancreatic encephalopathy
Acute intermittent porphyria

Endocrinopathy

Hyperthyroidism, hypothyroidism
Cushing's syndrome
Adrenal cortical insufficiency
Pituitary failure

Nutritional deficiency

Wernicke's encephalopathy
Pellagra
Vitamin B_{12} deficiency

Intoxication

Acute alcohol intoxication
Alcohol withdrawal
Opioid intoxication
Cocaine intoxication
Amphetamine intoxication
Phencyclidine intoxication
Sedative-hypnotic intoxication
Sedative-hypnotic withdrawal
Barbiturate intoxication
Barbiturate withdrawal
Benzodiazepine intoxication
Benzodiazepine withdrawal
Lithium intoxication
Carbon monoxide poisoning

Medications

Hemorrhage

Intracranial hemorrhage
- SAH
  - Aneurysm
  - Arteriovenous malformation
  - Disseminated intravascular coagulation

CNS trauma

Acute subdural hematoma
Subacute subdural hematoma
Epidural hematoma
SAH
Concussion
Contusion

Vascular

Transient ischemic attack
Cerebral infarction
Vasculitis
Venous occlusion

Tumors

CNS
- Primary
- Metastatic
- Meningeal carcinomatosis

Paraneoplastic
- Limbic encephalitis

Seizures

Generalized
Partial
Postconvulsive

TABLE 1.1 Causes of Delirium (Continued)

Miscellaneous	Temperature dysregulation
Hypertensive encephalopathy	Sensory deprivation
Beclouded dementia	Sleep deprivation
Postoperative delirium	Hydrocephalus
Cardiac bypass	

D. Endocrinopathy manifests as abnormalities of multiple organ systems and usually has a subacute onset.
E. Nutritional deficiencies most often (in the United States) affect patients with alcoholism, systemic cancer, and malabsorption syndromes.
F. Intoxication with and **withdrawal** from illicit drugs and alcohol can be life threatening and necessitate prompt recognition and timely intervention.
G. Medications cause delirium among patients who have impaired renal and liver function or interference with metabolism from other drugs especially those with anticholinergic and dopaminergic properties.
H. Hemorrhage and infarction in the CNS that cause delirium usually are associated with focal neurologic signs and are an emergency, frequently necessitating neurosurgical intervention.
I. CNS trauma can cause concussion, brain contusion, and epidural and subdural hematoma, each potentially manifesting as a confused state with associated focal neurologic features.
J. Vascular causes usually manifest as focal neurologic signs.
1. Lesions localizing to particular areas of the posterior circulation and right hemisphere may manifest as confusional states.
K. CNS tumors, malignant and benign, primary and metastatic, can cause prominent changes in mental status, including confusion, focal neurologic findings, headaches, and signs of increased intracranial pressure (ICP).
L. Seizures and postconvulsive states are common causes of intermittent confusion.
M. Hypertensive encephalopathy should be considered in patients with extreme hypertension and mental status changes.
N. Beclouded dementia and **postoperative delirium** are encountered frequently by physicians practicing in a general medical setting.
1. Patients with dementia are particularly sensitive to infections, metabolic abnormalities, and medications that may cause delirium.

II. CLINICAL MANIFESTATIONS

A. Mental status. Examination of a delirious patient is challenging.
1. Histories must be interpreted with skepticism. Seek information from families and friends.
2. Prodromal symptoms can develop abruptly or over hours to days, with resolution occurring in days to weeks. Hour-to-hour fluctuations of mental status are common.
3. Understanding the premorbid functioning of patients may assist in the diagnosis and prognosis, especially if the patient has an underlying structural pathologic condition.
4. The history and physical examination should be performed in a quiet room.
5. Avoid distractions or interruptions.
6. Restraints should be avoided if it can be done safely.
7. Engage the patient in a friendly and polite manner. Note whether the patient follows a logical progression of thoughts.
8. Frequent topic changes can signify confusion and avoid frustrating questions.
   a. **Attention.** The hallmark of delirium is the inability to maintain selective attention to the environment and mental processes.
   b. **Orientation.** Delirious patients often are disoriented to time and place but oriented to person.

c. **Arousal.** Changes in level of arousal are common, ranging from agitation with increased alertness to somnolence.
d. **Memory.** Because registration depends on the ability to focus attention, delirious patients frequently are unable to form new memories and do so only during lucid periods.
e. **Perception.** Impairment of both qualitative and quantitative perception is common for delirious patients. Hallucinations usually are either visual or auditory. Illusions and delusions are prominent.
f. **Disordered thinking.** Abnormalities of cognitive processing and problem solving are common.
g. **Emotional disturbances.** Marked emotional lability and inappropriate emotional responses occur frequently.
h. **Language abnormalities.** The inattention and distractibility of delirium challenges meaningful interaction and communication with others. The verbal output of delirious patients tends to be rambling and incoherent. Aphasia often is mistaken for confusion.
i. **Disturbances of the sleep–wake cycle** are common. Patients may remain awake for most of the day and night with only brief naps or may reverse their normal sleep pattern. The nocturnal exacerbation of confusion ("sundowning") is common.

B. Other neurologic findings.

1. **Papilledema** is a sign of increased ICP or hypertensive encephalopathy. However, its absence does not rule out an increase in ICP.
2. **Pupillary changes.**
   a. Fixed and dilated pupils occur with anticholinergic (e.g., atropine and scopolamine) intoxication.
   b. Enlarged but reactive pupils are present with increased sympathetic activity, intoxication with amphetamines or cocaine, and therapeutic use of epinephrine and norepinephrine as pressor agents.
   c. Midposition unreactive pupils can be caused by glutethimide overdose or focal midbrain dysfunction, often from distortion by an expanding supratentorial mass.
   d. Use of opioids is associated with constriction of the pupils (<2 mm).
   e. The presence of a unilaterally dilated pupil with or without the other components of third cranial nerve palsy is a sign of brainstem distortion. *This is a neurologic emergency* until proved otherwise and necessitates immediate diagnosis and treatment.
3. Abnormalities of **ocular motility** associated with confusion usually signal the presence of either increased ICP or brainstem distortion.
   a. Upgaze palsy suggests a lesion of the dorsal upper midbrain or distortion due to hydrocephalus.
   b. Unilaterally impaired eye adduction (with pupillary dilation) and diminished consciousness represent a third nerve palsy, which is a *neurologic emergency*.
   c. Delirium with **quadriparesis** can occur as a result of central pontine myelinolysis (CPM), progressive multifocal leukoencephalopathy (PML), and acute disseminated encephalomyelitis (ADEM).
   d. Delirium with **paraparesis** can occur with cryptococcosis, vitamin B_{12} deficiency, and ADEM.
   e. Cushing's disease and hypokalemia can manifest as **proximal muscular weakness.**
4. The presence of **abnormal limb movement** often is helpful in determining the cause of delirium.
   a. **Myoclonus** is asynchronous irregular twitching of a single muscle, groups of muscles, or entire limbs, usually with proximal predominance. It can be associated with metabolic abnormalities, hypoxic-ischemic injury, lithium intoxication, and CNS infections.
   b. **Asterixis** is recurrent brief lapses of posture observed with arms raised and elbows and wrists extended. It is a common manifestation of hepatic encephalopathy and uremia.
   c. The **tremor** most frequently observed with delirium is coarse and irregular, most prominent in the fingers of the extended arms and absent at rest, and most

commonly associated with hyperthyroidism, intoxication with sympathomimetics (amphetamine, cocaine, and phencyclidine), alcohol intoxication and withdrawal, and barbiturate and benzodiazepine withdrawal.

d. **Gait ataxia** is prominent with intoxication, vitamin B_{12} deficiency, syphilis, and Wernicke's encephalopathy.

e. **Seizures** can cause confusion and often signify a structural brain abnormality, metabolic abnormality, or intoxication or withdrawal state.

(1) **Partial complex seizures** are the most common type of focal seizures that can cause confusion. Although rarely encountered, **epilepsia partialis continua** is a focal motor epilepsy whereby clonic movements of the face, arm, and leg recur intermittently for long periods of time.

(2) **Generalized seizures** can cause confusion or postconvulsive encephalopathy.

(3) **Absence seizures** are generalized seizures that induce brief lapses of consciousness with prominent automatisms.

III. EVALUATION

The neurologic findings of delirium are discussed in II.B.

A. The history is the most important part of the evaluation. Often family members and other observers must be the primary historian for delirious patients.

1. Headache. Acute headache reported by a confused patient can signify a severe intracranial pathologic condition such as subarachnoid hemorrhage (SAH) or intraparenchymal hemorrhage, whereas progressive headaches are more suggestive of a CNS neoplasm, infection, or hydrocephalus.

2. Previous brain damage. Patients with cerebral infarction, progressive neurologic disease, psychiatric illness, head trauma, or previous neurosurgical procedures are predisposed to delirium, often in association with other neurologic signs.

3. Preexisting medical conditions such as cardiac and lung disease are risk factors for life-threatening conditions that cause delirium.

4. Drug history. When evaluating a delirious patient, the clinician should always obtain a detailed substance abuse history.

5. Exposure history. Inquiries should be made about exposure to meningitis, HIV, carbon monoxide, and other potential CNS toxins.

6. Medications. Addition of new medications or changes of dosage frequently are associated with confusion.

B. General physical examination.

1. Abnormalities of vital signs often herald a medical emergency.

a. **Hypotension** from dehydration, sepsis, cardiac arrhythmia, or congestive heart failure must be recognized and controlled.

b. **Tachycardia** can be a manifestation of infection, cardiac abnormality, hyperthyroidism, dehydration, withdrawal states, intoxication with sympathomimetic drugs, or sympathetic overactivity from delirium.

c. **Hypoventilation** related to pneumonia or drug overdose can result in hypoxia or hypercapnia.

d. **Increases in body temperature** are associated with infection, withdrawal states, and hyperthyroidism. Hypothermia is associated with sepsis and barbiturate overdose.

2. Nuchal rigidity is a sign of meningeal irritation as frequently occurs with CNS infection and SAH. **Meningitis, encephalitis,** and **SAH** should be pursued diagnostically in the presence of nuchal rigidity or if clinical suspicion is high even in its absence.

3. In all cases of confusion, there should be a search for **evidence of head trauma** such as scalp laceration, depressed skull fracture, or hemotympanum.

4. Purulent drainage from the nares or a **gray and immobile tympanic membrane** can represent sinusitis or otitis media, respectively. The nasal septum should be examined for erosions due to cocaine use.

5. The **skin** should be examined for cyanosis, hirsutism, hyperpigmentation, and scaly dermatitis. The clinician should inspect the skin of all patients for the presence of track or "pop" marks, which imply intravenous drug use.

6. **Examination of the heart** can reveal murmurs and irregular rhythms that predispose patients to cerebral circulatory compromise.
7. **Decreased or absent breath** sounds can be caused by congestive heart failure or pneumonia, the resulting hypoxia potentially contributing to delirium.
8. Patients with **abdominal tenderness** should be evaluated for intraabdominal infection. Neurosurgical patients with a ventriculoperitoneal shunt can have shunt infection that manifests as abdominal peritonitis.
9. Patients with delirium from hepatic failure can have **ascites, splenomegaly, spider telangiectasia, caput medusae, icteric sclera,** and **jaundice.**

C. Ancillary tests.

1. Measurement of serum levels of **electrolytes, glucose, blood urea nitrogen,** and **creatinine, complete blood cell count** (with differential), **liver enzymes, prothrombin** and **partial thromboplastin times,** and **arterial blood gases** with arterial ammonia level cover all of the metabolic abnormalities that must be urgently identified.
2. **A drug screen** and a **blood alcohol level** should be included.
3. If the results of the foregoing laboratory tests are negative, **HIV, fluorescent treponemal antibody-absorption, thyroid function,** and **cortisol stimulation tests** are needed.
4. An **ECG** to rule out arrhythmia and cardiac ischemia and a **chest radiograph** to rule out infections (e.g., pneumonia) that contribute to delirium or pulmonary processes that can compromise ventilation and oxygenation should be obtained.

D. Lumbar puncture. If meningitis or encephalitis is suspected, CSF analysis is mandatory. CSF examination is also indicated if findings at CT of the brain are negative in cases of suspected SAH. Routine CSF analysis consists of WBC count with differential and RBC count, glucose and total protein, and Gram stain and culture. Often, patients with delirium need more than the basic CSF studies.

1. **Contraindications to lumbar puncture.**
   a. Coagulopathy or platelet count <50,000 mm^3.
   b. Loss of cisternal spaces, evidence of brainstem distortion, absent or distorted fourth ventricle, and any posterior fossa mass on a CT scan.
   c. Abscess over the lumbar puncture site.
   d. Clinical suspicion of an intracranial mass lesion or increased ICP.
2. The **CSF WBC count** is considered abnormal when more than four WBCs of any type or one neutrophil are found. An increased WBC count suggests CNS infection.
   a. Neutrophils predominate in bacterial infection of the CNS and in early viral encephalitis, particularly that caused by enteroviruses.
   b. Lymphocytes predominate in tuberculous and cryptococcal meningitis, syphilitic infection, herpes simplex encephalitis, toxoplasmosis, and HIV infection.
3. The presence of **any RBCs** in the CSF is abnormal and requires explanation. Traumatic tap is the most common cause.
   a. Two important pathologic processes that increase the RBC count include SAH and herpes simplex encephalitis. Cerebral infarction, brain tumor (primary and metastatic), traumatic hematoma, and nontraumatic intracerebral hemorrhage inconsistently increase the RBC in the CSF.
   b. **Xanthochromia** is yellow color caused by the presence of **oxyhemoglobin** and **bilirubin** from lysed RBCs in the supernatant of centrifuged CSF.
4. A normal **CSF glucose** level is >50% of the serum glucose level. A low CSF glucose occurs with CNS infection, SAH, hepatic failure, and hypoglycemia.
5. Increases in **CSF protein** level occur with CNS infection, hemorrhage, and obstruction of CSF flow.
   a. Assuming a normal concentration of serum proteins, CSF protein level increases 1 mg per 1,000 RBCs. If a higher ratio is present, the presence of a pathologic process should be suspected.
6. **CSF Gram stain and cultures** should be performed on all CSF specimens. In cases of suspected bacterial meningitis, latex agglutination testing provides rapid identification of some common bacterial antigens.
7. **PCR** analysis can assist with the identification of CNS infection due to organisms not readily grown on culture media (e.g., viruses).

8. **CSF cryptoccocal antigen staining** can be used to rapidly determine the presence of cryptococci. Fungal cultures are more sensitive.
9. **CSF cytologic evaluation** is used to screen for carcinomatous meningitis, CNS lymphoma, and intracellular toxoplasmosis.

E. Neuroimaging.

1. **CT** can help identify most causes of delirium that involve structural damage to the brain, including intraparenchymal, epidural, subdural, and SAH, tumors, infarction, hydrocephalus, and edema.
   a. The CT scan may be normal in cases of early cerebral infarction, meningitis, or hemorrhage of low volume or if the patient has severe anemia.
   b. Intravenous contrast material should be administered for cases of suspected brain abscess or tumor. If the patient's condition is stable, MRI should be performed instead of CT with contrast material.
2. **MRI of the brain** is useful in the evaluation of delirious patients with suspected herpes simplex encephalitis, white matter processes (e.g., ADEM), a posterior fossa mass, multiple lesions (e.g., metastasis and septic emboli), or immunosuppression.
3. **Magnetic resonance angiography (MRA)** and **venography (MRV)** of the brain are noninvasive diagnostic studies used to diagnose many conditions that affect the vasculature of the brain. Aneurysms, arteriovenous malformations, dissection of large vessels, cerebral venous sinus occlusion, and stenosis and occlusion of both intracranial and extracranial vessels often can be detected with MRA/MRV. Conventional angiography is more sensitive than is MRA/MRV for the diagnosis of CNS vascular disease.
4. **Angiography** should be considered when aneurysm, arteriovenous malformation, venous occlusive disease, or CNS vasculitis is suspected.

F. EEG has a role in the evaluation of delirious patients.

1. Almost all patients with delirium have an abnormal EEG with either a posterior dominant rhythm frequency of > 8 Hz or a relative decrease from an alpha wave of 12 to 10 Hz with mild encephalopathy. As the encephalopathy worsens, the background becomes disorganized, and high-voltage theta and delta activity (slowing) appears with loss of EEG reactivity at frequencies > 5 to 6 Hz.
2. EEG helps in the diagnosis of complex partial status epilepticus and absence seizures.
3. Specific EEG patterns such as triphasic waves or high-voltage slowing with sharp waves on a flat background can be seen.

G. Brain biopsy is rarely indicated for the evaluation of delirium. It is necessary when histologic typing of CNS tumors will affect management and outcome and in cases of suspected CNS vasculitis or abscess if the risks of empiric therapy outweigh the risks of the procedure.

IV. DIFFERENTIAL DIAGNOSIS

Certain conditions can masquerade as delirium (Table 1.2), often requiring an experienced clinician to differentiate the actual process from delirium. Accurate diagnosis is imperative for proper prescription of therapy.

A. Aphasia. Language formulation disturbance (aphasia) can be initially misdiagnosed as confusion. Because other focal abnormalities (e.g., visual field defects, hemiparesis, and hemisensory loss) frequently accompany aphasia more than they do delirium, focal examination findings should drive a thorough "ruling-out" of aphasia.

TABLE 1.2 Differential Diagnosis of Delirium

Aphasia
Mania
Psychosis
Depression
Dementia
Transient global amnesia

B. Psychiatric disorders usually are characterized by prominent changes in several aspects of the mental status examination. Examples include mania, depression, and schizophrenia. A manic patient has a consistently elevated mood, increased goal-directed activity, and grandiosity. In contrast, a delirious patient has emotional lability and is unable to complete tasks.

C. Dementia. Patients with dementia have memory impairment out of proportion to other aspects of the mental status examination.

D. Transient global amnesia usually occurs among middle-aged or elderly persons and is an acute, self-limited episode of amnesia that lasts for several hours. The memory deficit is for the present and recent past. The key features of delirium are notably absent.

V. DIAGNOSTIC APPROACH

In the evaluation of a patient with delirium, a logical, stepwise approach enables the clinician to rapidly and accurately diagnose the underlying cause.

A. On presentation, consider causes such as hypotension and hypoxia that are an immediate threat to life.

B. If oxygenation and circulation are adequate, a neurologic examination for signs of increased ICP, intracranial hemorrhage, cerebral infarction, tumor, or CNS infection should be performed. If the findings at examination are abnormal, emergency CT of the brain should be performed. If available, MRI or the brain should be considered if the patient has no contraindications and is medically stable.

C. On arrival, admission tests should be performed to rule out a metabolic, cardiac, or toxic cause.

D. EEG should be performed to rule out ictal activity, if seizures are suspected.

E. CT and EEG should be performed if all laboratory results are negative.

F. A lumbar puncture should be performed, if there are no contraindications, if CT and EEG have not led to a diagnosis.

G. MRI should be performed if the clinician suspects that a structural lesion exists despite normal CT findings or if encephalitis, a white matter process, multiple lesions, or a posterior fossa mass is suspected or the patient is immunosuppressed.

VI. CRITERIA FOR DIAGNOSIS

The diagnosis of delirium or acute confusion is given to any patient for whom the predominate abnormalities at mental status examination are inattention and a decline in general cognitive functioning. The *Diagnostic and Statistical Manual of Mental Disorders-IV*[1] lists the following criteria for the diagnosis of delirium due to a general medical condition:

A. Disturbance of consciousness (e.g., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.

B. A change in cognition (e.g., memory deficit, disorientation, and language disturbance) or the development of a perceptual disturbance that is not better accounted for by preexisting, established, or evolving dementia.

C. A disturbance that develops over a short time, usually hours to days, and tends to fluctuate during the course of the day.

D. Evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition.

[1]From the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, revised. Washington, DC: American Psychiatric Association, 2000. Reprinted with permission.

Recommended Readings

Britton CB, Miller JR. Neurological complications in acquired immunodeficiency syndrome (AIDS). *Neurol Clin*. 1984;2:315–339.

Brown TM. Drug-induced delirium. *Semin Clin Neuropsychiatry*. 2000;5:113–124.

Fann JR. The epidemiology of delirium: a review of studies and methodological issues. *Semin Clin Neuropsychiatry*. 2000;5:64–74.

Griggs RC, Satran R. Metabolic encephalopathy. In: Rosenberg RN, ed. *Comprehensive Neurology*. New York, NY: Raven Press; 1991.

Lipowski ZJ. Delirium in the elderly patient. *N Engl J Med*. 1989;320:578–582.

Marcantonio ER, Rudolph JL, Culley D, et al. Serum biomarkers for delirium. *J Gerontol A Biol Med Sci*. 2006;61(12):1281–1286.

Mesulam MM, Waxman SG, Geschwind N, et al. Acute confusional states with right middle cerebral artery territory infarctions. *J Neurol Neurosurg Psychiatry*. 1976;29:84–89.

Miller MO. Evaluation and management of delirium in hospitalized older patients. *Am Fam Physician*. 2008;78(11): 1265–1270.

Taylor D, Lewis S. Delirium. *J Neurol Neurosurg Psychiatry*. 1993;56:742–751.

Thompson TL, Thompson WL. Treating postoperative delirium. *Drug Ther*. 1983;13:30.

Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Semin Clin Neuropsychiatry*. 2000;5:132–148.

Vasilevskis EE, Ely EW, Speroff T, et al. Reducing iatrogenic risks: ICU-acquired delirium and weakness—crossing the quality chasm. *Chest*. 2010;138(5):1224–1233.

Whitley RJ, Soong SJ, Linneman C Jr, et al. Herpes simplex encephalitis: clinical assessment. *JAMA*. 1982;247:317–320.

CHAPTER 2

Approach to the Patient with Dementia

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In the *Diagnostic and Statistical Manual of Mental Disorders-IV* (*DSM-IV*) criteria, **dementia** is defined as a decline in memory and at least one other cognitive function (aphasia, apraxia, agnosia, or a decline in an executive function, such as planning, organizing, sequencing, or abstracting). This decline impairs social or occupational functioning in comparison with previous functioning. The deficits should not occur exclusively during the course of delirium and should not be accounted for by another psychiatric condition, such as depression or schizophrenia. Dementia is further defined by a possible, probable, or definite etiologic diagnosis. The *DSM-IV* definition of dementia harbors the caveats that it may exclude debilitating cognitive disorders with predominant nonmemory presentation. Furthermore, minimally demanding environments may mask diagnosis of dementia.

I. EPIDEMIOLOGY OF DEMENTIA

It is estimated that the worldwide prevalence of dementia in 2010 is 4.7% in people aged >60, amounting to >35 million patients. The prevalence estimates vary from 2.6% in Africa to 6.5% in the Americas. The two most common types of dementia are Alzheimer's disease (AD) and vascular dementia (VaD), accounting for 50% to 75% and 15% to 25% of all dementia cases, respectively. The global incidence of dementia is estimated to be approximately 7.5 per 1,000 population, increasing exponentially from 1 per 1,000 person years for ages 60–64 to >70 per 1,000 person years in 90+ year olds. The number of people with dementia is expected to increase to 65.7 million in 2030 and 115.4 million in 2050, unless new therapies that delay its onset or progression are developed. Thus, the public and socioeconomic impact of dementia is a significant worldwide problem.

II. RISK FACTORS AND ETIOLOGY

A. Risk factors. The following have been identified as risk factors for the development of dementia and/or AD in one or more studies: Nonmodifiable risk factors proposed for dementia and/or AD are increasing age, female sex, unfavorable perinatal conditions, early life development, and growth. Modifiable risk factors fall into vascular and psychosocial categories. According to the vascular hypothesis, the following are modifiable risk factors for dementia: hypertension, obesity, hyperlipidemia, diabetes mellitus, heart disease (peripheral atherosclerosis, heart failure, and atrial fibrillation), cerebrovascular disease, heavy alcohol intake, and cigarette smoking. According to the psychosocial hypothesis, the following may be the socioeconomically modifiable risk factors for dementia: low education, poor social network, low mental or physical activity. The following have been proposed as potential protective factors for dementia, although their roles are yet to be proven in clinical trials: Statins, B group vitamins, "Mediterranean diet," nonsteroidal anti-inflammatory agents, antioxidants, omega 3 fatty acids, physical and mental exercise, and treating sleep disorders.

B. Etiology. Table 2.1 lists many of the causes of dementia. Potentially reversible conditions were identified in 4% to 8% of dementia cases in different studies. Hydrocephalus, space-occupying lesions, psychiatric disease, medications, alcoholism, and substance abuse were the most frequent causes of nondegenerative and nonvascular dementia. Although treatment for the potentially reversible conditions may not lead to partial or full reversal of dementia, their identification and attempted treatment is crucial.

Table 2.2 lists the degenerative causes of dementia by pathologic classification. Table 2.3 includes the syndromic classification of degenerative dementias. It is important to acknowledge that the same underlying pathology may present as different clinical syndromes, and different pathologies may present as the same clinical syndrome. Despite this, the existing clinicopathologic correlations allowed for the development of diagnostic criteria for degenerative and VaDs, discussed below.

TABLE 2.1 Causes of Dementia

Degenerative (see Tables 2.2 and 2.3)

Vascular
Multiple infarction
Single stroke
Binswanger's disease
Vasculitis
Subarachnoid hemorrhage
Amyloid angiopathy
Hereditary cerebral hemorrhage with angiopathy—Dutch type
CADASIL
Subdural hematoma

Infectious
Meningitis (fungal, mycobacterial, and bacterial)
Syphilis
AIDS dementia
Creutzfeldt–Jakob's disease
Post-herpes simplex encephalitis
Lyme's disease
Whipple's disease
Progressive multifocal leukoencephalopathy

Autoimmune/inflammatory
Systemic lupus erythematosus
Sjögren's disease
Multiple sclerosis
Steroid responsive encephalopathy
Paraneoplastic

Tumors
Glioblastoma
Lymphoma
Metastatic tumor

Toxic/metabolic
Vitamin B_{12} deficiency
Thyroid deficiency
System failure: liver, renal, cardiac, and respiratory
Heavy metals
Toxins (e.g., glue sniffing)
Electrolyte abnormalities
Hypoglycemia
Parathyroid disease
Drugs
Alcohol

Traumatic
Closed head injury
Open head injury
Pugilistic brain injury
Anoxic brain injury

Psychiatric
Depression
Personality disorder
Anxiety disorder

Other
Symptomatic hydrocephalus

Italics indicate the etiologic factor is at least partially reversible or treatable.

TABLE 2.2 Degenerative Dementias: Pathologic Classification

Amyloid/tau

AD

Tau
Pick's disease
Corticobasal degeneration
Progressive supranuclear palsy
Frontotemporal dementia with parkinsonism linked to chromosome 17 (tau mutations)
Tangle-only dementia
Argyrophilic grain disease

α-synuclein
Lewy's body disease
Parkinson's disease dementia
Multisystem atrophy

Tau-/Ubiquitin+
TDP-43+
FTLD with ubiquitin (FTLD-U) ± motor neuron disease (±progranulin, valosin containing protein mutations)
TDP-43–
Neuronal intermediate filament inclusion disease
Basophilic inclusion body disease
FTLD-U with CMP2B mutation

Other
Huntington's disease
Dementia lacking distinctive histologic features
Progressive subcortical gliosis

TABLE 2.3 Degenerative Dementias: Syndromic Classification

MCI (progressive amnestic syndrome)	Frontotemporal dementia
Single domain	PPA
Amnestic	Progressive nonfluent aphasia
Non-amnestic	Semantic dementia and associative agnosia
Multiple domain	Corticobasal degeneration syndrome
Amnestic	Posterior cortical atrophy
Non-amnestic	

III. CRITERIA FOR DIAGNOSIS

The following are the diagnostic guidelines for AD, VaD, dementia with Lewy's bodies (DLB), and frontotemporal lobar degeneration (FTLD) (the four most common causes of dementia in order). Also presented are the guidelines for diagnosis of mild cognitive impairment (MCI), which bridges the spectrum between dementia and normal cognition.

A. Alzheimer's disease. AD is characterized by both amyloid and tau pathology. The **National Institute of Neurological and Communicative Disorders and Stroke** and the **Alzheimer's and Related Diseases Association** 1984 criteria for the diagnosis of AD have recently been modified to take into account (1) Patients with the pathophysiologic process of AD, which can be found in those with normal cognition, MCI, and AD. This pathophysiologic process designated as AD-P is thought to begin years before the diagnosis of clinical AD. (2) The diagnostic criteria of other diseases such as Lewy's body disease and frontotemporal dementia. (3) MRI, positron emission tomography (PET) for imaging the amyloid beta protein (Aβ), ^{18}fluorodeoxyglucose (FDG) PET, and the CSF biomarkers Aβ42, total tau and phophotau. (4) Other clinical syndromes that do not present with amnesia but are related to AD pathology including posterior cortical atrophy and logopenic aphasia. (5) The dominantly inherited AD causing mutations in amyloid precursor protein, presenilin-1, and presenilin-2 (*APP*, *PSEN1*, *PSEN2*, respectively). (6) A change in age cut-offs noting persons under 40 and over 90 may have the same AD-P. (7) Many persons with possible AD in the past are now designated MCI.

Below we present the 1984 criteria for probable and possible AD. Patients who meet the 1984 criteria for probable AD still meet criteria for probable AD. Additionally, we present the proposed new 2011 criteria for AD in III.A.8.

1. Criteria for the clinical diagnosis of probable AD.

a. Dementia established by means of clinical examination and documented with the Mini-Mental State Examination, Blessed Dementia Rating Scale, or other similar examination and confirmed with neuropsychological tests.
b. Deficits in two or more areas of cognition.
c. Progressive worsening of memory and other cognitive function.
d. No disturbance of consciousness.
e. Onset between the ages of 40 and 90 years, most often after 65 years.
f. Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

2. Supporting findings in the diagnosis of probable AD.

a. Progressive deterioration of specific cognitive functions such as aphasia, apraxia, or agnosia.
b. Impaired activities of daily living and altered patterns of behavior.
c. Family history of similar disorders, particularly if confirmed neuropathologically.
d. Laboratory results as follows:
   (1) Normal results of lumbar puncture (LP) as evaluated with standard techniques.
   (2) Normal or nonspecific EEG changes (increased slow-wave activity).
   (3) Evidence of cerebral atrophy at CT with progression documented by means of serial observation.

3. Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD.

a. Plateaus in the course of progression of the illness.

b. Associated symptoms of depression; insomnia; incontinence; delusions; illusions; hallucinations; catastrophic verbal, emotional, or physical outbursts; sexual disorders; and weight loss.
c. Other neurologic abnormalities for some patients, especially those with advanced disease, and including motor signs such as increased muscle tone, myoclonus, or gait disorder.
d. Seizures in advanced disease.
e. CT findings normal for age.

4. **Features that make the diagnosis of probable AD uncertain or unlikely.**
   a. Sudden, apoplectic onset.
   b. Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness.
   c. Seizures or gait disturbance at the onset or early in the course of the illness.
5. **Clinical diagnosis of possible AD.**
   a. May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia and with variations in onset, presentation, or clinical course.
   b. May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the principal cause of the dementia.
   c. Should be used in research studies when a single, gradually progressive, severe cognitive deficit is identified in the absence of any other identifiable cause.
6. **Criteria for the diagnosis of definite AD** are the clinical criteria for probable AD and histopathologic evidence obtained from a biopsy or autopsy.
7. **Classification of AD for research purposes** should specify features that differentiate subtypes of the disorder such as familial occurrence, onset before 65 years of age, presence of trisomy 21, and coexistence of other relevant conditions such as Parkinson's disease.
8. **Proposed new criteria for AD.** In 2011, National Institute on Aging and the Alzheimer's Association workgroup suggested new criteria for AD based on clinical and research evidence. All patients who met the 1984 criteria for probable AD described in III.A.1 would meet the current criteria. In addition, the following criteria are proposed:
   a. **Probable AD dementia with increased level of certainty.** This category includes patients with "probable AD dementia with documented decline" and "probable AD dementia in a carrier of a causative AD genetic mutation in *APP*, *PSEN1*, or *PSEN2* genes."
   b. **Possible AD dementia.** This category includes patients with an "atypical course" or "mixed etiology" and would not necessarily meet the 1984 criteria for possible AD. "Atypical course" is characterized by "sudden onset, insufficient historical detail or objective cognitive documentation of progressive decline." "Mixed etiology" includes subjects with concomitant cerebrovascular disease or features of DLB or "evidence for another neurologic disease or a non-neurologic medical comorbidity or medication use that could have a substantial effect on cognition."
   c. **Probable or possible AD dementia with evidence of the AD pathophysiologic process.** These criteria are proposed only for research purposes and incorporate the use of biomarkers, which are not yet advocated for routine diagnostic use. These biomarkers fall into the two categories of "brain amyloid ß (A ß) protein deposition," that is low CSF Aß42 and positive PET amyloid imaging; and "downstream neuronal degeneration or injury," that is elevated CSF tau, decreased FDG uptake on PET in temporoparietal cortex, and disproportionate atrophy on structural MRI in medial, basal, and lateral temporal lobe, and medial parietal cortex. The biomarker profile will fall into clearly positive, clearly negative, and indeterminate categories.

B. Vascular dementia. There are different published diagnostic criteria for VaD: NINDS-AIREN (National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et L'Enseignement en Neurosciences), ADDTC (State of California Alzheimer's Disease Diagnostic and Treatment Centers), *DSM-IV*, and Hachinski Ischemia Scale. Their distinct features lead to differences in sensitivity and specificity. The first set of criteria discussed below is the **NINDS-AIREN criteria for** VaD and is as follows:

1. **The criteria for probable VaD include all of the following:**
   a. Dementia defined similarly to *DSM-IV* criteria.
   b. Cerebrovascular disease defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski's sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant cerebrovascular disease at brain imaging (CT or MRI), including multiple large-vessel infarcts or a single strategically situated infarct (angular gyrus, thalamus, basal forebrain, or posterior or anterior cerebral artery territories), as well as multiple basal ganglia and white matter lesions and white matter lacunes or extensive periventricular white matter lesions, or combinations thereof.
   c. A relation between the two previous disorders manifested or inferred from the presence of one or more of the following: (1) onset of dementia within 3 months after a recognized stroke, (2) abrupt deterioration in cognitive functions, or (3) fluctuating, stepwise progression of cognitive deficits.
2. **Clinical features consistent with the diagnosis of probable VaD include the following:**
   a. Early presence of a gait disturbance.
   b. History of unsteadiness and frequent, unprovoked falls.
   c. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease.
   d. Pseudobulbar palsy.
   e. Personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits, including psychomotor retardation and abnormal executive functioning.
3. **Features that make the diagnosis of VaD uncertain or unlikely include the following:**
   a. Early onset of memory and other cognitive functions, such as language, motor skills, and perception in the absence of corresponding lesions at brain imaging.
   b. Absence of focal neurologic signs other than cognitive disturbance.
   c. Absence of cerebrovascular lesions on CT scans or MRIs.
4. **The term AD with cerebrovascular disease** should be reserved to classify the condition of patients fulfilling the clinical criteria for possible AD and who also have clinical or brain imaging evidence of relevant cerebrovascular disease.
5. **The criteria for definite VaD are as follows:**
   a. Probable VaD, according to core features.
   b. Cerebrovascular disease by histopathology.
   c. Absence of neurofibrillary tangles or neuritic plaques exceeding those expected for age.
   d. Absence of other clinical or pathologic disorders capable of producing dementia.
6. Vascular dementia: **ADDTC criteria** for VaD are as follows:
   a. The criteria for probable VaD include all of the following:
      (1) Dementia by *DSM-III-R* criteria.
      (2) Two or more strokes by history/examination and/or CT or T1-weighted MRI or single stroke with clear temporal relationship to onset of dementia.
      (3) Presence of at least one infarct outside cerebellum by CT or T1-weighted MRI.
   b. The criteria for possible VaD include all of the following:
      (1) Dementia by *DSM-III-R* criteria.
      (2) Single stroke with temporal relationship to dementia or Binswanger defined as the following: (1) early onset incontinence or gait disturbance not explained by peripheral cause, (2) vascular risk factors, and (3) extensive white matter changes on neuroimaging.
   c. The criteria for mixed dementia are as follows:
      (1) Evidence of AD or other disease on pathology exam plus probable, possible, or definite ischemic VaD.
      (2) One or more systemic or brain diseases contributing to patient's dementia in the presence of probable, possible, or definite ischemic VaD.
   d. The criteria for definite ischemic VaD are as follows:
      (1) Dementia.
      (2) Multiple infarcts outside the cerebellum on neuropathology exam.

7. Vascular dementia: ***DSM-IV* criteria** for VaD are as follows:
   a. Impaired memory.
   b. Presence of at least one of the following: aphasia, apraxia, agnosia, or impaired executive functioning.
   c. Symptoms impair work, social, or personal functioning.
   d. Symptoms do not occur solely during delirium.
   e. Cerebral vascular disease has probably caused the above deficits, as judged by laboratory data or by focal neurologic signs and symptoms.
8. Vascular dementia: Hachinski Ischemic Scale for VaD assigns points to each criterion. A total score >7 corresponds to multi-infarct dementia, whereas <4 is interpreted as AD. Below, each criterion is shown with the associated number of points in parentheses.
   a. Abrupt onset (2).
   b. Stepwise progression (1).
   c. Fluctuating course (2).
   d. Nocturnal confusion (1).
   e. Relative preservation of personality (1).
   f. Depression (1).
   g. Somatic complaints (1).
   h. Emotional incontinence (1).
   i. History of hypertension (1).
   j. History of strokes (2).
   k. Associated atherosclerosis (1).
   l. Focal neurologic symptoms (2).
   m. Focal neurologic signs (2).

C. **DLB** is defined pathologically by the presence of cortical Lewy's bodies mainly composed of α-synuclein and is part of a spectrum with Parkinson's disease, which has brainstem Lewy's bodies. The McKeith criteria for the clinical diagnosis of DLB are as follows:

1. Progressive cognitive decline interferes with normal social and occupational functioning.
2. Deficits on tests of attention, executive function, and visuospatial functioning often are prominent.
3. Prominent or persistent memory impairment may not be present early in the course of illness.
4. Two of the following core features are necessary for the diagnosis of **probable DLB** and one is necessary for **possible DLB**:
   a. Fluctuating cognition or alertness.
   b. Recurrent visual hallucinations.
   c. Spontaneous features of parkinsonism.
5. **Suggestive features.** ≥1 suggestive feature + ≥1 core feature are sufficient for the diagnosis of probable DLB; ≥1 suggestive feature and no core features are sufficient for diagnosis of possible DLB; probable DLB should not be diagnosed based on suggestive features alone.
   a. REM sleep behavior disorder.
   b. Severe neuroleptic sensitivity.
   c. Low-dopamine transporter uptake in basal ganglia demonstrated by single photon emission computed tomography (SPECT) or PET imaging.
6. **Features supportive of the diagnosis** are repeated falls, syncope or transient loss of consciousness, severe autonomic dysfunction, tactile or olfactory hallucinations, systematized delusions, depression, relative preservation of mesial temporal lobe structures on CT/MRI, reduced occipital activity on SPECT/PET, low uptake MIBG myocardial scintigraphy, prominent slow wave activity on EEG with temporal lobe transient sharp waves.
7. **The following features suggest a disorder other than DLB:**
   a. Cerebrovascular disease evidenced by focal neurologic signs or cerebral infarcts present on neuroimaging studies.
   b. The presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture.
   c. If parkinsonism only appears for the first time at a stage of severe dementia.

8. **Temporal sequence of symptoms.** DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease.

D. FTLD involves focal atrophy of the frontal or temporal lobes or both, the distribution of atrophy determining the clinical presentation. The age at onset tends to be slightly younger (often before 65 years) than that for AD. Patients with clinical FTLD usually do not have Alzheimer's-type pathologic findings and instead have other distinct pathology. According to recent consensus recommendations, there are five major neuropathologic classifications for FTLD based on the presence of abnormally accumulating protein as follows: FTLD-tau (includes Pick's disease and FTDP-17), FTLD-TDP (transactive response DNA binding protein 43; includes familial FTLD due to mutations in *GRN*, *VCP*), FTLD-UPS (uniquitin proteasome system; includes familial FTLD due to mutations in *CHMP2B*), FTLD-FUS (fused in sarcoma; includes neuronal intermediate filament inclusion disease, basophilic inclusion body disease), and FTLD-ni (no inclusions).

The two major phenotypes of FTLD are behavioral variant (bvFTD) and primary progressive aphasia (PPA). Three main variants of PPA are defined as nonfluent/agrammatic, semantic, and logopenic. International bvFTD Criteria Consortium (FTDC) presented their first report on the comparison of 1998 Neary et al. criteria and their proposed criteria by Rascovsky et al. at the 2011 Annual American Academy of Neurology meeting, which identified greater sensitivity. The proposed 2011 FTDC criteria for bvFTD need further evaluation and are as follows: *Possible bvFTD* requires three of six clinically discriminating features (disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/compulsive behaviors, hyperorality, and dysexecutive neuropsychological profile). *Probable bvFTD* also includes functional disability and characteristic neuroimaging; and *bvFTD with Definite FTLD* requires histopathologic evidence of FTLD or a pathogenic mutation.

In comparison, the 1998 **Neary's criteria** for the clinical diagnosis of bvFTLD are as follows:

1. **In frontotemporal dementia,** character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well-preserved. Core criteria are as follows:
   a. Insidious onset and gradual progression.
   b. Early decline in social interpersonal conduct.
   c. Early impairment in regulation of personal conduct.
   d. Early emotional blunting.
   e. Early loss of insight.
2. Supportive diagnostic features of FTD are as follows:
   a. Decline in personal hygiene and grooming.
   b. Mental rigidity and inflexibility.
   c. Distractibility and impersistence.
   d. Hyperorality and dietary changes.
   e. Perseverative and stereotyped behavior.
   f. Utilization behavior.
   g. Speech and language features: aspontaneity and economy of speech; press of speech, stereotypy of speech, echolalia, perseveration, and mutism.
   h. Physical signs: primitive reflexes, incontinence, akinesia, rigidity, tremor, low and labile blood pressure.
   i. Investigations: Neuropsychology-significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder; EEG-normal; imaging-predominant frontal or anterior temporal abnormality.

Gorno-Tempini et al. have provided new classification and criteria for the PPA variants. It should be noted that while most PPA-nonfluent/agrammatic variant has FTLD-tau, most PPA-semantic variant has FTLD-TDP and most PPA-logopenic variant has AD pathology, a definitive clinicopathologic correlation cannot be established. Thus the following criteria represent clinical classifications.

1. Diagnosis of **PPA requires that the following criteria be met.**
   a. Difficulty with language as the most prominent clinical feature.
   b. Daily activities impaired primarily due to language impairment.
   c. Aphasia as the most prominent early deficit.
   d. Deficit not accounted for by other disorders.
   e. Deficit not accounted for by psychiatric diagnosis.
   f. No prominent initial episodic memory, visual impairments.
   g. No prominent initial behavioral disturbance.
2. Clinical diagnosis of **PPA-nonfluent/agrammatic variant.**
   At least one of the following core features must be present:
   a. Agrammatism in language production.
   b. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech).
   At least two of three of the following other features must be present:
   a. Impaired comprehension of syntactically complex sentences.
   b. Spared single-word comprehension.
   c. Spared object knowledge.
3. Imaging-supported **PPA-nonfluent/agrammatic variant diagnosis.**
   Both of the following criteria must be present:
   a. Clinical diagnosis of nonfluent/agrammatic variant PPA.
   b. Imaging must show one or more of the following results:
      (1) Predominant left posterior frontoinsular atrophy on MRI.
      (2) Predominant left posterior frontoinsular hypoperfusion or hypometabolism on SPECT or PET.
4. **PPA-nonfluent/agrammatic variant with definite pathology.**
   Clinical diagnosis (criterion a below) and either criterion b or c must be present.
   a. Clinical diagnosis of nonfluent/agrammatic variant PPA.
   b. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, and others).
   c. Presence of a known pathogenic mutation.
5. Clinical diagnosis of **PPA-semantic variant.**
   Both of the following core features must be present:
   a. Impaired confrontation naming.
   b. Impaired single-word comprehension.
   At least three of the following other diagnostic features must be present.
   a. Impaired object knowledge, particularly for low frequency or low-familiarity items.
   b. Surface dyslexia or dysgraphia.
   c. Spared repetition.
   d. Spared speech production (grammar and motor speech).
6. Imaging-supported **PPA-semantic variant diagnosis.**
   Both of the following criteria must be present:
   a. Clinical diagnosis of semantic variant PPA.
   b. Imaging must show one or more of the following results:
      (1) Predominant anterior temporal lobe atrophy.
      (2) Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET.
7. **PPA-semantic variant with definite pathology.**
   Clinical diagnosis (criterion a below) and either criterion b or c must be present.
   a. Clinical diagnosis of semantic variant PPA.
   b. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, and others).
   c. Presence of a known pathogenic mutation.
8. Clinical diagnosis of **PPA-logopenic.**
   Both of the following core features must be present.
   a. Impaired single-word retrieval in spontaneous speech and naming.
   b. Impaired repetition of sentences and phrases.

At least three of the following other features must be present:
a. Speech (phonologic) errors in spontaneous speech and naming.
b. Spared single-word comprehension and object knowledge.
c. Spared motor speech.
d. Absence of frank agrammatism.

9. Imaging-supported **PPA-logopenic** diagnosis.
Both criteria must be present.
a. Clinical diagnosis of logopenic variant PPA.
b. Imaging must show at least one of the following results:
(1) Predominant left posterior perisylvian or parietal atrophy on MRI.
(2) Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET.

10. **PPA-logopenic with definite pathology.**
Clinical diagnosis (criterion a below) and either criterion b or c must be present.
a. Clinical diagnosis of **PPA-logopenic.**
b. Histopathologic evidence of a specific neurodegenerative pathology (e.g., AD, FTLD-tau, FTLD-TDP, and others).
c. Presence of a known pathogenic mutation.

E. MCI is the transitional state between normal aging and dementia and represents a condition with greater rate of progression to dementia than normal aging. Patients with amnestic MCI progress to AD at a rate of 10% to 15% per year. Initial criteria for MCI required the presence of memory impairment. Current criteria also recognize non-amnestic forms of MCI.

1. **Criteria for MCI are as follows.** Cognitive impairment that is not normal for aging, represents a decline, does not reach criteria for dementia, and does not impair activities of daily living.
2. **Subtypes of MCI are as follows.** Depending on the presence or absence of memory impairment and presence of one or more cognitive impairments, there are four types of MCI. Memory impairment present: amnestic MCI versus non-memory cognitive impairment: non-amnestic MCI. Single domain (one domain impaired only) versus multiple domain. It is proposed that the expected outcome of single or multiple domain amnestic MCI is AD, of single or multiple domain non-amnestic MCI is less likely to be AD, although this is possible, and could be FTD or DLB.
3. **New proposed research criteria for MCI.** These criteria incorporate the use of biomarkers as described in III.A.8.c. When both A β and neuronal injury biomarkers are "positive" in a subject with MCI, it is suggested that these subjects have the highest likelihood of progressing to AD dementia, hence the terminology of "MCI due to AD-High likelihood" is proposed. When only one set of biomarkers is positive, "MCI due to AD-Intermediate likelihood" and when both are negative "MCI-Unlikely due to AD" is suggested. Additional work is needed for the validation of these criteria and standardization of biomarkers.

IV. EVALUATION

A. History. It is essential that the history be obtained not only from the patient but also from an independent informant. In most the patient can be told, "I am now going to ask your spouse some questions, and if your spouse makes any errors, feel free to make corrections." Sometimes the informant may not want to speak openly in front of the patient, so the clinician may want to arrange a separate interview, perhaps while the patient is undergoing another test or later by telephone.

1. **Patient difficulties.** Determine what difficulties the patient is having and what family members have noticed. Commonly a patient with dementia may not know there is a memory difficulty or be able to give accurate details of the problem. Begin by asking the patient an open-ended question such as, "What problems are you having?" This often does not elicit the desired responses. Even with specific questions such as, "Are you having difficulty with your memory?" the clinician may not be told what the problems are.

The informant may have to be asked specific questions, such as, "What can't the patient do now that he (or she) could do before?" or "Does the patient sometimes ask the same question more than once in the same conversation?"

2. **Time course.** The time the family first noticed problems and the course the disease has taken over time are critical factors in the evaluation. A disease that is slowly progressive fits the profile of a degenerative disease such as AD. A disease that starts suddenly or follows a stepwise progression would be more in keeping with VaD. Rapidly progressive dementia (over a few months) suggests Creutzfeldt–Jakob's disease.
3. **Functioning of the patient.** Determine how well the patient has been functioning at work and at home, including performance of the basic activities of daily living. Patients with MCI are by definition able to function well. Patients with progressive nonfluent aphasia or semantic dementia usually also are able to function well. Ask what the patient does to keep busy. Does he or she read the newspaper, watch the news on television, keep the checkbook, do the shopping, prepare the meals, take part in a sport or hobby? Knowing this information helps in the planning of questions to ask during the mental status part of the examination.
4. **Issues of safety.** Ask whether the patient drives. If so, has the patient ever become lost while driving or had any accidents, near-accidents, or traffic violations? If the patient prepares meals, has he or she ever left the stove on? Does the patient keep weapons, and if so, has this posed any danger to the patient or to others?
5. **Etiologically directed history.** Include a history of vascular disease and risk factors, head injury, toxic exposure, symptoms of infection or exposure to diseases such as tuberculosis, psychiatric history such as depression, symptoms of depression (such as a change in weight, insomnia, crying, or anhedonia), medications, systemic illnesses, other past illnesses, and alcohol or tobacco use.

   The following questions may bring out symptoms of DLB: Does the patient have good days and bad days? What specifically cannot the patient do on bad days? Does the patient see things that are not there (visual hallucinations)? Does the patient act out dreams at night (rapid eye movement sleep disorder)? Look for personality and behavioral changes in FTD with specific questions such as, Does the patient drive recklessly, such as run stop signs or speed? Has the patient developed poor table manners such as eating excessively fast? Does the patient have rituals or do things repetitively?
6. **Family history.** Ask what the patient's parents died of and at what ages. Ask specifically whether there were memory problems in the later years. Then ask about the ages and health of the patient's siblings and children. Patients with late-onset AD commonly have a family history of disease. A strong family history for a younger patient suggests an autosomal dominant disease such as familial AD, familial FTLD, Huntington's disease, or spinocerebellar ataxia.

B. Physical examination.

1. Give a standardized short mental state test, such as the Folstein Mini-Mental State Examination or the Short Test of Mental Status. Asking about news events is a highly sensitive measure of recent memory. Be sure that the patient has been exposed to this information. Ask questions such as, Who is the president? What is his wife's name? Who was the last president? What is his wife's name? Note any evidence of aphasia, apraxia, or agnosia. Anomia with preservation of orientation suggests semantic dementia. Observe for lack of insight and disinhibited behaviors that occur in frontotemporal dementia.
2. Look for cardiovascular risk factors such as hypertension, arterial bruits, arrhythmia, and heart murmur.
3. Complete a full neurologic examination. Pay special attention to focal deficits such as visual field cuts, paresis, sensory loss, and ataxia. Posterior cortical atrophy, which most commonly has Alzheimer's-type pathology begins as progressive visual dysfunction similar to that of Balint's syndrome. Evaluate for any extrapyramidal difficulties, such as hypokinesia, increased muscle tone, a masklike face, and micrographia. Determine whether the patient has any problem in walking. This is often best undertaken in the hallway rather than in the examining room. Note the patient's step size, speed of walking, arm swing, and ability to turn. The palmomental reflex and snout reflex are not particularly helpful because they are common among healthy elderly. The grasp reflex occurs late in the course of the disease.

C. Laboratory studies.

1. **Recommended in all cases** are CBC, chemistry panel, erythrocyte sedimentation rate, thyroid and liver function tests, folate and vitamin B_{12} levels, syphilis serologic testing, CT or MRI, and neuropsychological evaluation.
2. **Recommended selectively** are electroencephalography, LP, chest radiograph, HIV test, drug screen, SPECT or PET, heavy metal screen, copper, or ceruloplasmin.
3. **Electroencephalography** can be useful in diagnosing Creutzfeldt–Jakob's disease, differentiating depression or delirium from dementia, evaluating for encephalitis, revealing seizures as causes of memory difficulties, and diagnosing nonconvulsive status epilepticus.
4. **LP** is recommended if the patient has cancer, infection is a possibility, hydrocephalus is seen at imaging, the patient is younger than 55 years, the dementia is acute or subacute, the patient is immunosuppressed, or vasculitis or connective tissue disease is suspected.
5. **PET** or **SPECT** can be useful in differentiating frontotemporal dementia from AD. In one blinded study in which PET was used to evaluate patients with and those without dementia, the sensitivity was only 38% and the specificity was 88%.
6. **Numerous diagnostic biomarkers** for degenerative diseases are becoming available; however, the positive predictive value of these biomarkers in a typical clinical scenario is uncertain. CSF amyloid β and τ protein levels jointly are reported to be 89% sensitive and 90% specific for AD. We use this test only when a LP is being performed for other reasons, such as evaluation for hydrocephalus. In the Scandinavian countries, CSF amyloid β and τ protein levels are being used to distinguish patients with MCI at risk of developing AD. CSF 14-3-3 protein is reported to be 94% sensitive and 93% specific for Creutzfeldt–Jakob's disease compared with neurologic controls, but false-positive and false-negative results do occur (and are probably more likely in atypical cases, in which it would be the most useful). The $\epsilon 4$ allele of the apolipoprotein E gene (apoE4) is a well-established risk factor for AD; however, the American Medical Association does not recommend apoE4 testing in the diagnosis of AD or if the patient's condition is presymptomatic. Mutations in the *PSEN1*, *PSEN2*, and *APP* genes can cause early-onset, autosomal dominant AD. Only mutations in *PSEN1* are commercially available for testing, and genetic counseling is required before and after testing. Structural imaging techniques including voxel-based morphometry, hippocampal volumetric measurement; functional imaging techniques including f-MRI, magnetic resonance spectroscopy and direct amyloid imaging in the brain are emerging as imaging techniques with potential use for differentiating various dementia types and for preclinical diagnoses. As mentioned above, these biomarkers are included in the new criteria for pre-symptomatic AD, MCI and AD dementia, though additional research is needed for their validation and standardization.

V. DIFFERENTIAL DIAGNOSIS

Be aware of the possible causes of dementia in Table 2.1. The most important reversible causes include depression, medication, hydrocephalus, thyroid disease, vitamin B_{12} deficiency, fungal infection, neurosyphilis, subdural hematoma, and brain tumor.

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Recommended Readings

Albert MS, Dekosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270–279.

Alzheimer's Association. 2011 Alzheimer's disease facts and figures. *Alzheimers Dement J Alzheimers Assoc*. 2011;7(2):208–244.

Alzheimer's Disease International. World Alzheimer report 2010: the global economic impact of dementia. http://www.alz.co.uk/research/world-report. Published September 21, 2010. Accessed July 14, 2011.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.

Becker P, Feussner JR, Mulrow CD, et al. The role of lumbar puncture in the evaluation of dementia: the Durham Veterans Administration/Duke University Study. *J Am Geriatr Soc*. 1985;33:392–396.

Boeve BF. Diagnosis and management of the non-Alzheimer dementias. In: Noseworthy JH, ed. *Neurological Therapeutics: Principles and Practice*. London, UK: Martin Dunitz; 2003.

Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. *Ann Neurol.* 2003;54(suppl 5):S15–S19.

Cairns NJ, Bigio EH, Mackenzie IR, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta Neuropathol (Berl)*. 2007;114(1):5–22.

Consensus report of the Working Group on: "Molecular and Biochemical Markers of Alzheimer's Disease." The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group. *Neurobiol Aging*. 1998;19:109–116.

Corey-Bloom J, Thal LJ, Galasko D, et al. Diagnosis and evaluation of dementia. *Neurology*. 1995;45:211–218.

Ertekin-Taner N. Genetics of Alzheimer's disease: a centennial review. *Neurol Clin*. 2007;25(3):611–667.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.

Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76(11):1006–1014.

Graff-Radford NR, Godersky JC, Jones M. Variables predicting surgical outcome in symptomatic hydrocephalus in the elderly. *Neurology*. 1989;39:1601–1604.

Hejl A, Hogh P, Waldemar G. Potentially reversible conditions in 1000 consecutive memory clinic patients. *J Neurol Neurosurg Psychiatry*. 2002;73(4):390–394.

Kalaria RN, Maestre GE, Arizaga R, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol*. 2008;7(9):812–826.

Knopman DS, Petersen RC, Cha RH, et al. Incidence and causes of nondegenerative nonvascular dementia: a population-based study. *Arch Neurol*. 2006;63(2):218–221.

Kokmen E, Naessens JM, Offord KP. A short test of mental status: description and preliminary results. *Mayo Clin Proc*. 1987;62(4):281–288.

Mackenzie IR, Neumann M, Bigio EH, et al. Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. *Acta Neuropathol*. 2010;119(1):1–4.

McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65(12):1863–1872.

McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*. 1984;34:939–944.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263–269.

Morris JC, ed. *Handbook of Dementing Illnesses*. New York, NY: Marcel Dekker; 1994.

Mortimer JA. The epidemiology of Alzheimer's disease: beyond risk factors. In: Iqbal K, Mortimer JA, Winblad B, Iqbal K, Mortimer JA, Winblad B,Wisniewski HM (eds). et al., eds. *Research Advances in Alzheimer's Disease and Associated Disorders*. New York, NY: John Wiley & Sons; 1995:3–11.

Neary D, Snowden J, Mann D. Frontotemporal dementia. *Lancet Neurol*. 2005;4(11):771–780.

Petersen RC. Mild cognitive impairment: current research and clinical implications. *Semin Neurol*. 2007;27(1):22–31.

Post SG, Whitehouse PJ, Binstock RH, et al. The clinical introduction of genetic testing for Alzheimer disease: an ethical perspective. *JAMA*. 1997;277:832–836.

Qiu C, De Ronchi D, Fratiglioni L. The epidemiology of the dementias: an update. *Curr Opin Psychiatry*. 2007;20(4):380–385.

Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250–260.

Seprling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280–292.

Thal LJ, Kantarci K, Reiman EM, et al. The role of biomarkers in clinical trials for Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2006;20(1):6–15.

Whitwell JL, Jack CR Jr. Neuroimaging in dementia. *Neurol Clin*. 2007;25(3):843–857.

CHAPTER 3

Approach to the Patient with Aphasia

Jeffrey L. Saver

Aphasia is a loss or impairment of language processing caused by brain damage. Language disorders are common manifestations of cerebral injury. Reflecting the centrality of language function in human endeavor, the aphasias are a major source of disability.

I. PATHOPHYSIOLOGY

A. Cerebral dominance. The left hemisphere is dominant for language in approximately 99% of right-handers and 60% of left-handers.

B. Neuroanatomy. A specialized cortical–subcortical neural system surrounding the Sylvian fissure in the dominant hemisphere subserves language processing (Fig. 3.1). Circumscribed lesions in different components of this neurocognitive network produce distinctive syndromes of language impairment.

II. ETIOLOGY

A. Stroke. Cerebrovascular disease is a frequent cause of aphasia. The perisylvian language zone is supplied by divisions of the middle cerebral artery, a branch of the internal carotid artery. The classic aphasic syndromes are most distinctly observed in ischemic stroke because vascular occlusions produce discrete, well-delineated brain lesions.

B. Other focal lesions. Any focal lesion affecting the language cortices will also produce aphasia, including primary and metastatic neoplasms and abscesses. **Primary progressive aphasia** is a neurodegenerative syndrome characterized by slowly progressive, isolated language impairment in late life and focal atrophy of dominant frontotemporal cortices. Affected individuals frequently develop a generalized dementia after the first 2 years of illness. Among the causes of primary progressive aphasia are (1) frontotemporal lobar dementia due to tauopathy and (2) a focal variant of Alzheimer's disease (AD).

C. Diffuse lesions. Diseases producing widespread neuronal dysfunction will disrupt language processing along with other cognitive and noncognitive neural functions. **Traumatic head injury** and **AD** are epidemiologically common causes of aphasic symptoms, although not of isolated aphasia.

III. CLINICAL MANIFESTATIONS

A. Nonfluency versus fluency. Fluency refers to the rate, quantity, and ease of speech production. In nonfluent speech, verbal output is meager (<50 words per minute), phrase length shortened (1 to 4 words per phrase), production effortful, articulation often poor, and the melodic contour (prosody) disturbed. Nonfluent speakers often preferentially employ substantive nouns and verbs, eliding small connecting grammatical/functor words ("telegraphic speech"). Conversely, in fluent speech, verbal output is generous (and may even be more abundant than customary), phrase length normal, production easy, articulation usually preserved, and the melodic contour intact.

1. **Anatomic correlate.** Nonfluency indicates damage to the frontal language regions anterior to the fissure of Rolando. Fluency signals that these areas are intact.

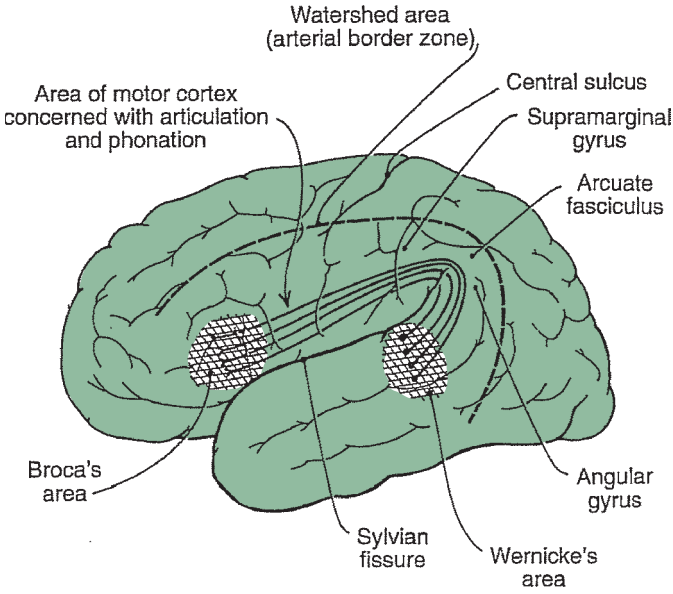

FIGURE 3.1 The neurocognitive network for language. The core perisylvian language cortices lie within the dashed line and include Broca's area in the inferior frontal gyrus, the supramarginal and angular gyri in the parietal lobe, the subjacent arcuate fasciculus white matter tract, and Wernicke's area in the superior temporal gyrus. Extrasylvian sites that produce transcortical aphasias are found in surrounding cortices (beyond dashed line). (Modified with permission from Mayeux R, Kandel ER. Disorders of language: the aphasias. In: Kandel ER, Schwartz JH, Jessell TM, eds. *Principles of Neural Science*. 3rd ed. New York, NY: Elsevier; 1991.)

B. Auditory comprehension impairment. Impaired ability to understand spoken language ranges from complete mystification by simple one-word utterances to subtle failure to extract the full meanings of complex sentences. In informal conversation, aphasic patients often capitalize on clues from gestures, tone, and setting to supplement their understanding of the propositional content of a speaker's utterances. Examiners may underestimate the extent of auditory comprehension impairment if they fail to test formally a patient's comprehension deprived of nonverbal cues.

1. **Anatomic correlate.** Comprehension impairment generally reflects damage to the temporoparietal language regions posterior to the fissure of Rolando. Preserved comprehension indicates that these areas are intact. (Comprehension of grammar is an important exception to this rule. Agrammatism is associated with damage to inferior frontal language regions.)

C. Repetition impairment. Repetition of spoken language is linguistically and anatomically a distinct language function. In most patients, repetition impairment parallels other deficits in spoken language. Occasionally, however, relatively isolated disordered repetition may be the dominant clinical feature (conduction aphasia). In other patients, repetition may be well-preserved despite severe deficits in spontaneous speech (transcortical aphasias). Rarely, such patients exhibit echolalia, a powerful, mandatory tendency to repeat all heard phrases.

1. **Anatomic correlate.** Impaired repetition indicates damage within the core perisylvian language zone. Preserved repetition signals that these areas are intact.

D. Paraphasic errors. Substitutions of incorrect words for intended words are paraphasias. Paraphasic errors are classified into three types.

1. A **literal** or **phonemic paraphasia** occurs when only a part of the word is misspoken, as when "apple" becomes "tapple" or "apfle."
2. A **verbal** or **global paraphasia** occurs when an entire incorrect word is substituted for the intended word, as when "apple" becomes "orange" or "bicycle." A **semantic paraphasia** arises when the substituted word is from the same semantic field as the

target word ("orange" for "apple"). Fluent output contaminated by many verbal paraphasias is **jargon speech**.

3. A **neologistic paraphasia** occurs when an entirely novel word not extant in the speaker's native lexicon is substituted for the intended word, as when "apple" becomes "brifun."
4. **Anatomic correlate.** Paraphasic errors may occur with lesions anywhere within the language system and do not carry strong anatomic implications. To some extent, phonemic paraphasias are more common with lesions in the frontal language fields and global paraphasias more common with lesions in temporoparietal areas.

E. **Word-finding difficulty (anomia).** Retrieval of target words from the lexicon is virtually always disturbed in aphasia. Patients may exhibit frequent hesitations in their spontaneous speech while they struggle with word-finding. **Circumlocutions** transpire when patients "talk around" words they fail to retrieve, providing lengthy definitions or descriptions to convey the meanings of words they are unable to access.

1. **Anatomic correlate**. Word-finding difficulty occurs with lesions located throughout the language-dominant hemisphere and possesses little localizing value.

F. **Reading and writing.** In most cases of aphasia, reading impairment (**alexia**) and writing impairment (**agraphia**) parallel oral language comprehension and production deficits. Occasionally, however, isolated reading impairment, writing impairment, or both can occur in the setting of fully preserved oral language function.

1. **Anatomic correlate.** The anatomy of reading and writing incorporates both the core perisylvian language zones and additional function-specific sites. Reading requires primary and higher-level visual processing in the occipital and inferior parietal lobes. Writing depends on visual stores in the inferior parietal lobe and graphomotor output regions in the frontal lobe.

IV. EVALUATION

A. **History.** Abrupt onset of language difficulty suggests a cerebrovascular lesion. Subacute onset may suggest tumor, abscess, or other more moderately progressive process. Slow onset suggests a degenerative disease, such as AD or frontotemporal lobar degeneration. Interviewing family members and other observers is crucial when the patient's language difficulty limits direct history-taking.

B. **Physical examination.**

1. **Elementary neurologic signs.** A detailed elementary neurologic examination allows identification of motor, sensory, or visual deficits that accompany the language disorder, aiding neuroanatomic localization. Important "neighborhood" signs are the presence or absence of hemiparesis, homonymous hemianopia or quadrantanopia, and apraxia.
2. **Mental status exam.** It is important to assess the patient's wakefulness and attentional function, lest language errors resulting from inattentiveness be wrongly ascribed to intrinsic linguistic dysfunction. Nonverbal tests to evaluate memory, visuospatial, and executive functions should be utilized if severe language disturbance precludes routine verbal assessment.
3. **Language exam**. A careful language exam is critical in the evaluation of aphasia, profiling the patient's impaired and preserved language abilities and allowing a syndromic, localizing diagnosis.
   a. **Spontaneous speech.** The patient's spontaneous verbal output, in the course of conversation and in response to general questions, should be judged for fluency versus nonfluency and presence or absence of paraphasias. It is important to ask open-ended questions such as "Why are you in the hospital?" or "What do you do during a typical day at home?" because patients may mask major language derangements with yes–no answers and other brief replies to more structured interrogatories.
   b. **Repetition.** The patient is asked to repeat complex sentences. If difficulty is evidenced, simpler verbal sequences from single-syllable words to multisyllabic words and short phrases are given to determine the level of impairment. At least one sentence rich in grammatical/functor words, such as "No ifs, ands, or buts," should be employed to test for isolated or more pronounced difficulty in grammatical repetition, as may be seen in Broca's and other anterior aphasias.

c. **Comprehension.** An initial judgment of auditory comprehension can be made in the course of obtaining the medical history and from spontaneous conversation. Tests that require no or minimal verbal responses are essential to the evaluation of auditory comprehension in individuals with severe disturbance of speech production and intubated patients.
   (1) **Commands.** One simple bedside test is verbally to instruct the patient to carry out one-step and multistep commands, such as "Pick up a piece of paper, fold it in half, and place it on the table." Cautions to recall when interpreting results are (1) apraxia and other motor deficits may cause impairment not related to comprehension deficit and (2) midline motor acts on command, such as closing/opening eyes and standing up, draw on distinct anatomic systems and may be preserved even in the setting of severe aphasic comprehension disturbance.
   (2) **Yes/no responses**. If the patient can reliably produce verbal or gestural yes/no responses, this output system may be used to assess auditory comprehension. Questions of graded difficulty should be employed for precise gauging of the degree of comprehension disturbance, using queries ranging from simple ("Is your name Smith?") to complex ("Do helicopters eat their young?").
   (3) **Pointing.** This simple motor response also permits precise mapping of comprehension impairment by means of questions of graded difficulty. The examiner should employ both simple pointing commands ("Point to the chair, nose, door") and more lexically and syntactically complex pointing commands ("Point to the source of illumination in this room").

d. **Naming.** Difficulty with naming is almost invariable in all the aphasia syndromes. Consequently, naming tasks are sensitive, although not specific, means of testing for the presence or absence of aphasia.
   (1) **Confrontation naming.** The patient is asked to name objects, parts of objects, body parts, and colors pointed out by the examiner. Common, high-frequency words ("tie," "watch") and uncommon, low-frequency words ("knot" of the tie, "watchband") should be tested.
   (2) **Word-list generation.** Another type of naming test is to ask the patient to generate a list of items in a category (animals, cars) or words beginning with a given letter (F, A, S). Normal individuals produce 12 or more words per letter in 1 minute.

e. **Verbal automatisms.** Patients with profound disruptions of speech production should be requested to produce (1) overlearned verbal sequences, including the numbers from 1 to 10 and the days of the week; (2) overlearned verbal material, such as the pledge of allegiance; and (3) singing, such as "Happy Birthday to You." These utterances draw on subcortical and nondominant hemisphere areas and indicate residual capacities in impaired patients that may be capitalized on in rehabilitation.

f. **Reading.** Patients should be asked to read sentences aloud. Written sentences that are commands ("Close your eyes") allow simultaneous testing of reading aloud and reading comprehension.

g. **Writing.** In the order of difficulty, patients may be asked to write single letters, words, and short sentences. Obtaining a signature is insufficient because this overlearned sequence may be retained when all other graphomotor function is lost.

C. Laboratory studies.

1. **CT.** A CT scan will delineate most focal structural lesions affecting the language regions of the brain. It may be normal in the first 24 hours following acute aphasia from new onset ischemic stroke.
2. **MRI.** An MRI is somewhat more sensitive than CT at detecting morphologic abnormalities and is the preferred study if readily available. Imaging in the sagittal and coronal as well as axial planes allows precise mapping of lesions within known neural language regions.

V. SYNDROMIC DIAGNOSIS

Distinctive features of a patient's language disturbance may be employed to assign a syndromic diagnosis that has localizing value. Eight classical cortical aphasia syndromes are distinguished

on the basis of fluency, comprehension, and repetition (Fig. 3.2). Approximately 60% of all aphasic patients exhibit one of these symptom clusters. Most of the remaining "atypical" aphasias will be found to harbor subcortical lesions. It is important to consider the time after onset when employing these syndromes for clinicoanatomic correlation. Soon after an acute insult, deafferentation, edema, hypoperfusion without infarction, and other mechanisms of diaschisis produce exaggerated clinical deficits. Later, neuroplasticity-mediated recovery of function reduces clinical deficits. The aphasia syndromes have maximal localizing value 3 weeks to 3 months after onset.

A. Perisylvian aphasias.

1. **Broca's aphasia.** Patients with Broca's aphasia exhibit (1) nonfluent, dysarthric, effortful speech; (2) similarly disordered repetition; and (3) relatively intact comprehension, with mild difficulty in understanding syntax and relational grammar. Their verbal output is often "telegraphic," containing substantive nouns and verbs but omitting small, connecting, functor words. Most patients exhibit a faciobrachial hemiparesis. Patients often exhibit frustration over their language deficits and are at elevated risk for depression.
   a. Lesions producing Broca's aphasia lie in the posterior portion of the inferior frontal gyrus (Broca's area) and extend to involve surrounding motor, premotor, and underlying white matter territories. Lesions restricted solely to Broca's area produce mild, transient aphasia and more persistent dysarthria.
   b. Broca's area is supplied by the superior division of the middle cerebral artery.
2. **Wernicke's aphasia.** Patients with Wernicke's aphasia evince fluent, effortless, well-articulated output, almost always contaminated with paraphasias and neologisms. Repetition demonstrates a parallel impairment, with fluent but paraphasic output. The leading feature of Wernicke's aphasia is a severe disturbance of auditory comprehension. Two types of behavioral responses to this comprehension deficit are observed. Most often in the acute phase, patients seem to be unaware of their inability to comprehend spoken language, calmly providing inappropriate and grossly paraphasic answers to observer's inquiries. Less frequently, patients are irritable and paranoic, perhaps

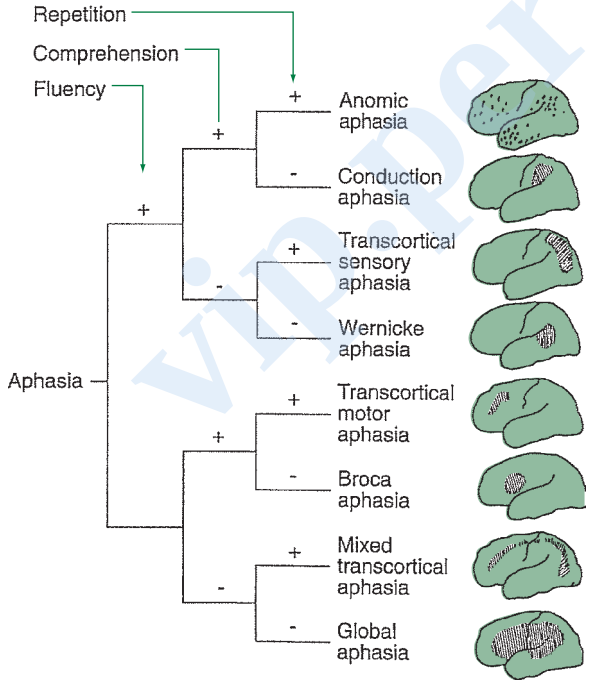

FIGURE 3.2 Algorithm for diagnosis and localization of the eight classical cortical aphasias.

because of their inability to understand what others say. A superior homonymous quadrantanopia is frequently present. However, the absence of more dramatic motor or sensory deficits, and the fluid production of speech, may mislead medical personnel into believing that the patient is confused or psychotic rather than aphasic, and may delay diagnosis while metabolic or psychiatric disturbances are sought.

a. The core of lesions engendering Wernicke's aphasia map to the posterior third of the superior temporal gyrus (Wernicke's area), an auditory association area. Lesion size may vary considerably, and damage often extends to the middle temporal gyrus and the inferior parietal lobe.
b. Wernicke's area is supplied by the inferior division of the middle cerebral artery.

3. **Global aphasia.** The most profound form of aphasia, called global aphasia, is characterized by drastically nonfluent output, severe disruption of comprehension, and little repetitive ability. Spontaneous speech is often absent initially, or marked by the production of a few stereotyped sounds. Patients neither read nor write. Hemiplegia is almost invariably present, and hemisensory loss and hemianopia are frequent.
   a. The typical insult involves the entire left perisylvian region, encompassing Broca's area in the inferior frontal lobe, Wernicke's area in the posterior temporal lobe, and all the interposed parietofrontal cortices. In rare cases, separate, discrete lesions of Broca's area and Wernicke's area produce global aphasia without hemiparesis.
   b. The perisylvian region lies within the territory of the middle cerebral artery, and internal carotid and middle cerebral artery occlusions are the most common causes of global aphasia.
4. **Conduction aphasia**. The hallmark of conduction aphasia is a disproportionate disruption of repetition. Comprehension of spoken language is relatively intact. Fluent spontaneous output is often marred by occasional hesitations and phonemic paraphasias, but is not as disturbed as repetition. Naming also tends to demonstrate mild paraphasic contamination. Motor and sensory disturbances are usually absent or mild.
   a. Two neural loci tend to give rise to conduction aphasia: (1) the supramarginal gyrus, sometimes with extension to the subinsular white matter and (2) the primary auditory cortex, insula, and subjacent white matter. The arcuate fasciculus, a subcortical white matter tract connecting Wernicke's and Brodmann's areas, is often, but not invariably, involved.
   b. These regions are variably supplied by branches of the inferior or superior divisions of the middle cerebral artery.

B. Extrasylvian aphasias. The extrasylvian aphasic syndromes share the clinical characteristic of preserved repetition and the anatomic trait of sparing of the core perisylvian language zone. They occur less commonly than the perisylvian aphasias. Many arise from watershed infarcts, but they may also appear in conjunction with tumors, abscesses, hemorrhages, and other lesions.

1. **Transcortical motor aphasia.** Transcortical motor aphasia is characterized by discrepant spontaneous speech and repetition. Spontaneous output is severely disrupted, nonfluent, and halting. In contrast, the ability to repeat sentences verbatim is preserved, as is reading aloud. Comprehension is undisturbed. Naming may be mildly impaired.
   a. **Transcortical motor aphasia** results from damage at one of two foci: (1) prefrontal cortices and subjacent white matter anterior or superior to Broca's area or (2) the supplementary motor area and cingulate gyrus. These lesions disconnect Broca's area from limbic areas and other sources of the drive to communicate.
   b. Lesions anterosuperior to Broca's area lie in the vascular border zone between the middle and anterior cerebral arteries. The supplementary motor area and cingulate gyrus regions are irrigated by the anterior cerebral artery.
2. **Transcortical sensory aphasia**. Patients with transcortical sensory aphasia exhibit severely disturbed comprehension of spoken language, but preserved repetition. Spontaneous speech is fluent, although often paraphasic. Echolalia—automatic repetition of overheard phrases—is common. Reading aloud may be fairly preserved, whereas reading comprehension is quite poor. Motor deficits are generally absent, but hemisensory deficits are common.
   a. Lesions may occur over a wide distribution posterior and superior to the posterior perisylvian region, including the middle temporal gyrus, the angular gyrus, and

underlying white matter. These insults disconnect Wernicke's area from multiple posterior association cortices, preventing retroactivation by aural word forms of the widely distributed neural representations that convey their meanings.

b. The lesions generally lie within the vascular watershed between the posterior and middle cerebral arteries.

3. **Mixed transcortical aphasia.** This rare and remarkable condition is analogous to global aphasia, except for preserved ability to repeat. Spontaneous speech is minimal or absent. Patients are unable to comprehend spoken language, name, read, or write. Repetition of spoken language, however, is preserved. Patients often are echolalic. Mild hemiparesis and hemisensory loss affecting proximal greater than distal extremities may be observed.

   a. Lesions are an additive combination of those producing transcortical motor and sensory aphasias. Insults anterosuperior to Broca's area and posterosuperior to Wernicke's area cut off the perisylvian language zone from access to other cortices. **Isolation of the speech area** is a synonym for mixed transcortical aphasia.

   b. The lesions fall in the crescentic vascular border zone among the anterior, middle, and posterior cerebral arteries.

4. **Anomic aphasia.** These patients exhibit difficulty retrieving verbal tags in spontaneous speech and confrontation naming. The remainder of language functions is relatively intact. Auditory comprehension, repetition, reading, and writing are normal. Spontaneous speech is preponderantly fluent, although interrupted by occasional hesitations for word-finding. In severe cases, output may be lengthy but empty, with recurrent circumlocutions.

   a. A wide variety of lesions, including both dominant and nondominant hemisphere loci, may produce anomic aphasia. Particularly common sources are insults to (1) the dominant inferior parietal lobe and (2) the dominant anterior temporal cortices. The latter insults have been associated with **category-specific naming deficits** in which naming in different semantic categories (e.g., living versus nonliving entities) is differentially impaired.

   b. The angular gyrus and anterior temporal cortices are supplied by different branches of the inferior division of the middle cerebral artery.

C. **Subcortical aphasia syndromes.** Focal lesions confined to subcortical structures strongly interconnected with language cortices produce aphasia. Although the optimal classification system for the subcortical aphasias is a still contested and unsettled enterprise, two major profiles can be discerned.

1. **Striatocapsular aphasia**. The language deficit in striatocapsular aphasia resembles that in anomic or transcortical motor aphasia. Patients may or may not be fluent but are almost invariably dysarthric. Mild to moderate anomia coexists with generally intact auditory comprehension, repetition, reading, and writing. Generation of complex syntactic sentences is impaired. Hemiparesis is common, hemisensory loss variable, and hemianopia infrequent. Lesions involve the dominant putamen, dorsolateral caudate, anterior limb of the internal capsule, and rostral periventricular white matter.

2. **Thalamic aphasia.** The language deficit in thalamic aphasia resembles that in transcortical sensory or mixed transcortical aphasia. Output may be nonfluent or relatively fluent, auditory comprehension is deficient, and repetition is preserved. Impairments of naming, reading comprehension, and writing are also present. A contralateral emotional facial paresis (diminished facial movement in expressing spontaneous emotions but preserved facial movements to command) and contralateral hypokinesia are often the only elementary neurologic deficits. Lesions are situated in the dominant anterolateral thalamus.

D. **Additional classical syndromes**. Strategically placed lesions may produce dissociated impairments of reading, writing, and oral language function. Three syndromes with well-characterized localizing properties will be reviewed.

1. **Alexia without agraphia (pure alexia)**. Reading is severely impaired, whereas spontaneous speech, repetition, and auditory comprehension are normal. Writing is preserved, but dramatically, after a delay, patients are unable to read phrases they themselves have written. Recognition of words spelled aloud and traced on the palm is normal. Only words presented visually pose difficulty. Patients frequently exhibit a slow, letter-by-letter reading strategy, painstakingly recognizing and stating aloud each letter in a word and then,

from the string of spoken letters, determining the target word. A right homonymous hemianopia is common but not invariable. Disorders of color vision, including achromatopsia and color anomia, may be present.

The most common neuroanatomic substrate comprises simultaneous lesions of the left occipital lobe and the splenium of the corpus callosum, depriving the angular gyrus region critical for word recognition of visual input from either the left or right hemisphere. The smallest sufficient injury is a single lesion of the paraventricular white matter of the mesial occipitotemporal junction (the forceps major), interrupting interhemispheric and intrahemispheric visual tracts to the angular gyrus but sparing the corpus callosum and left occipital cortex.

2. **Alexia with agraphia.** Patients exhibit loss of literacy—inability to read or write—but relatively well-preserved oral language function. Speech is fluent, although anomia is often present, and auditory comprehension and repetition are intact. Hemisensory deficits are frequent, and hemiparesis and hemivisual disturbances are variable. A full-fledged Gerstmann's syndrome, including dyscalculia, dysgraphia, left–right confusion, and finger agnosia, may be present.

   The underlying lesion involves the dominant inferior parietal lobule (angular and supramarginal gyri).

3. **Pure word deafness.** Patients resemble Wernicke's aphasics. Comprehension and repetition of spoken language are impaired, whereas speech is fluent. Unlike in Wernicke's patients, however, paraphasias are rare and, more importantly, comprehension of written material is intact. Writing production is also normal. Although uncomprehending of word sounds, patients have intact hearing and generally are successful in identifying meaningful nonverbal sounds such as car horns or telephone rings.

   Two types of lesions underlie pure word deafness, both disconnecting Wernicke's area from input from primary auditory cortices. Some patients harbor bilateral superior temporal lesions. A roughly equal number exhibit a single deep superior temporal lesion in the dominant hemisphere, blocking ipsilateral and crossing callosal auditory pathways.

E. **Aprosodia.** Meaning is conveyed not only through the propositional content of speech, but also through prosody—the melody, rhythm, timbre, and inflection of the speaker. Prosody is frequently disturbed in nonfluent aphasia. However, patients may have normal propositional language yet exhibit disturbances of the production, comprehension, or repetition of prosody. In general, the nondominant hemisphere plays a greater role in production and comprehension of emotional prosody than does the dominant hemisphere.

VI. DIFFERENTIAL DIAGNOSIS

Acquired speech impairments may result from disruption of lower-order neural and muscular mechanisms for implementing sound production rather than disturbances of central processing of language. It is important to distinguish these nonaphasic speech impairments from genuine aphasia, because they differ in their localizing significance and spectrum of etiologic causes.

A. **Dysarthria.** Dysarthria is abnormal articulation of spoken language. At least five types of nonaphasic dysarthria may be distinguished. (1) **Paretic dysarthria** is caused by weakness of articulatory muscles. Soft, low-pitched, nasal voicing is characteristic. Causes include myopathies, neuromuscular junction disorders such as myasthenia gravis, and lower motor neuron disease. (2) In **spastic dysarthria**, speech is typically strained, slow, and monotonic. Bilateral upper motor neuron lesions compromising the corticobulbar tracts are the cause. (3) In **ataxic dysarthria**, jerky irregular speech rhythm and volume are noted, reflecting lesions to the cerebellum or its connections. Multiple sclerosis is a common cause. (4) **Extrapyramidal dysarthrias** include hypokinetic dysarthria, which is seen in parkinsonism and choreic dysarthria, which is observed in Huntington's disease and other chorea syndromes. (5) In **aphemia (cortical dysarthria),** small lesions within Broca's area or the dominant frontal oral motor cortex produce dysarticulation without disturbing core language function.

   Aphasic dysarthria—dysarticulation occurring as one manifestation of an aphasic language syndrome—is common with anterior aphasias such as Broca's syndrome.

The nonaphasic dysarthrias may be distinguished from aphasic dysarthria by demonstrating preserved intrinsic language functions including naming, comprehension, and reading. Intact writing is most telling, showing normal productive language capacity when a nonoral output channel is employed.

B. Mutism. Aphasia—disordered language—can be securely diagnosed only on the basis of exemplars of disturbed output (or comprehension). Patients with acute onset aphasia, especially Broca's or global aphasia, are often unable to speak for the first few hours or days. However, a wide variety of other insults can produce total cessation of verbal output. The full differential diagnosis of mutism includes (1) psychiatric etiologies (schizophrenia, depression, catatonia, and psychogenic illness); (2) abulia/akinetic mutism (bilateral prefrontal, diencephalic, and midbrain lesions); (3) acute dominant supplementary motor area lesions; (4) pseudobulbar palsy; (5) locked-in syndrome from bilateral ventral pontine or midbrain lesions; (6) acute bilateral cerebellar lesions; (7) lower motor neuron lesions; and (8) laryngeal disorders.

C. Thought disorders. When an intact language apparatus is placed in service of an underlying thought disorder, bizarre utterances arise that superficially resemble the fluent aphasic output of patients with Wernicke's or conduction aphasia. Demographic features are helpful, recognizing that schizophrenia with psychotic speech of new onset tends to appear in individuals in their 20s and 30s, whereas fluent aphasias cluster in older individuals with vascular risk factors. Several features of the utterances also distinguish thought-disordered from fluent aphasic speech. (1) Paraphasias are common in aphasia but rare in schizophrenia. (2) The neologisms of aphasics are frequent and changing, whereas those of schizophrenics are infrequent and consistent. (3) Open-ended questions tend to prompt briefer responses in aphasics than in schizophrenics. (4) Bizarre and delusional themes appear only in schizophrenic discourse.

VII. COURSE

Some degree of spontaneous recovery of language function is invariable after a static brain injury. An initial accelerated period of improved function occurs over the first few days or weeks after insult and is attributable to resolution of edema, ischemic penumbra, and other causes of dysfunction at a distance from the site of permanent injury. The second, slower phase of recovery reflects utilization of parallel circuits, retraining, and structural neural plasticity. The bulk of this functional recovery takes place in the first 3 months after injury, and some may continue up to 1 year, rarely longer. Among the aphasia syndromes, the greatest recovery compared with baseline tends to occur in Broca's and conduction aphasias. Anomic aphasia is a common end stage into which other aphasia subtypes tend to evolve.

Factors favoring greater spontaneous improvement, as well as response to speech therapy, are young age, left-handedness or ambidexterity, higher education, smaller lesion size, no or few nonlanguage cognitive defects, absence of emotional difficulties such as depression and neglect, and strong family support. Patients with traumatic aphasia tend to recover more fully than patients with ischemic lesions.

VIII. REFERRAL

A. Neurologist. Most patients with aphasia should undergo neurologic consultation. The neurology specialist will confirm the presence of aphasia, clarify the type, aid in etiologic diagnosis, and provide the patient and family with an informed prognosis.

In selected cases, neurologists or physiatrists may consider pharmacotherapy of aphasia. Small case series have suggested that stimulants, cholinesterase inhibitors, dopamine antagonists, and other neurotransmitter modulators may augment language therapy. However, few randomized trials have been completed in this area. Recent small case series have also suggested that transcranial magnetic stimulation of the nondominant hemisphere may promote language recovery, by releasing the perilesional fields from tonic inhibition.

B. Speech and language pathologist. All patients with aphasia should have an evaluation by a speech and language pathologist. The speech therapist will perform a formal diagnostic assessment, profiling the patient's language strengths and weaknesses with normed tests. A variety of standardized language assessment batteries, including the Boston Diagnostic Aphasia Examination, the Western Aphasia Battery, the Porch Index of Communicative Ability, and the Communication Abilities in Daily Living, may be drawn on to survey a patient's abilities. The therapist then employs the results to design and implement an individualized treatment program of aphasia therapy.

Systematic language rehabilitation programs improve patient outcome. Treatment is tailored to each individual's pattern of linguistic and cognitive competencies and deficits, exploiting spared brain systems to reestablish, circumvent, or compensate for lost language capacities. A variety of deficit-specific programs are available to supplement general language stimulation. For nonfluency, treatments include (1) melodic intonation therapy, (2) sign language and other gestural communication training, and (3) communication boards. Syntax training may benefit agrammatism. Specific word-retrieval therapies have been developed for anomia and comprehension training programs for auditory comprehension deficits.

Speech therapy programs generally last for 2 to 3 months, in 30- to 60-minute sessions conducted 2 to 5 times per week. Recent studies suggest that intense treatment (at least 2 hours a day, at least 4 days per week) during a short period may be more effective than a similar number of sessions spread out over a longer time period. Self- and family-administered home exercises provide additional stimulation. Computer-based training is expanding in scope and sophistication.

C. Neuropsychologist. Patients who have major nonlinguistic cognitive deficits in addition to aphasia, and whose diagnosis is unclear, should undergo neuropsychological evaluation. Formal neuropsychological evaluation with tests that minimize language requirements allow a more detailed profiling of memory, visuospatial reasoning, executive function, praxis, and concept formation than can be obtained by bedside mental status examination. Findings may aid the physician in making a diagnosis by suggesting the pattern of neural system involvement and the speech pathologist in prescribing therapy by identifying the extent to which different extralinguistic capacities can support various compensatory strategies.

D. Patient support groups. The National Aphasia Association (National Aphasia Association, 350 Seventh Avenue, Suite 902, New York, NY 10001, 1-800-922-4622, www.aphasia.org) is an excellent resource for patients and their families. The American Heart/Stroke Association and National Stroke Association also provide beneficial programs and information.

Recommended Readings

Alexander MP, Hillis AE. Aphasia. *Handb Clin Neurol*. 2008;88:287–309.

Blair M, Marczinski CA, Davis-Faroque N, et al. A longitudinal study of language decline in Alzheimer's disease and frontotemporal dementia. *J Int Neuropsychol Soc*. 2007;13:237–245.

Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu Rev Neurosci*. 2002;17:151–188.

Broca P. Remarks on the seat of the faculty of articulate speech, followed by the report of a case of aphemia (loss of speech). In: Rottenberg DA, Hochberg FH, eds. *Neurologic Classics in Modern Translation*. New York, NY: Hafner; 1977:136–149.

Catani M, Jones DK, Ffytche DH. Perisylvian language networks of the human brain. *Ann Neurol*. 2005;57:8–16.

Damasio H, Tranel D, Grabowski TJ, et al. Neural systems behind word and concept retrieval. *Cognition*. 2004;92:179–229.

Flamand-Roze C, Falissard B, Roze E, et al. Validation of a new language screening tool for patients with acute stroke: the Language Screening Test (LAST). *Stroke*. 2011;42:1224–1229.

Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76:1006–1014.

Hillis AE. Aphasia: progress in the last quarter of a century. *Neurology*. 2007;69:200–213.

Kelly H, Brady MC, Enderby P. Speech and language therapy for aphasia following stroke. *Cochrane Database Syst Rev*. 2010;(5):CD000425.

LaPointe L, ed. *Aphasia and Related Neurogenic Language Disorders*. 4th ed. New York, NY: Thieme; 2011.

Wildgruber D, Ackermann H, Kreifelts B, et al. Cerebral processing of linguistic and emotional prosody: fMRI studies. *Prog Brain Res*. 2006;156:249–268.

CHAPTER 4

Approach to the Patient with Memory Impairment

Daniel Tranel, Natalie L. Denburg, and Torricia H. Yamada

The term **amnesia** refers to conditions in which patients lose, partly or completely, the ability to learn new information or to retrieve information acquired previously. Amnesia (also referred to here as *memory impairment* or *memory dysfunction*) is common in neurologic diseases that affect the telencephalon or diencephalon and is a defining characteristic and frequently an early manifestation of some of the most frequently encountered neurologic diseases, including Alzheimer's disease (AD). As such, reports of memory impairment must be taken seriously.

Accurate diagnosis and effective management of memory disorders are important. A considerable clinical challenge is presented, however, by the facts that the most frequent neurologic diseases affect elderly persons and a certain degree of decline in memory is associated with normal aging. Hence, it can be difficult to differentiate reports of memory problems that may be normal manifestations of aging versus a signal of the presence of neurologic disease. Memory problems are common in nonneurologic conditions such as psychiatric disease, and this constitutes another reason for careful diagnosis. Such distinctions often require laboratory testing that can be conducted by neuropsychological assessments.

I. TYPES OF MEMORY AND MEMORY SYSTEMS IN THE BRAIN

There are several fundamental distinctions between different types of memory and the neural systems to which different types of memory are related (Table 4.1).

A. Anterograde and retrograde memory.

1. **Anterograde memory** refers to the capacity to learn new information—that is, to acquire new facts, skills, and other types of knowledge. It is closely dependent on neural structures in the mesial temporal lobe, especially the hippocampus and interconnected structures, such as the amygdala, the entorhinal and perirhinal cortices, and other parts of the parahippocampal gyrus.
2. **Retrograde memory** refers to the retrieval of information that was acquired previously—that is, retrieval of facts, skills, and other knowledge learned in the recent or remote past. This type of memory is related to nonmesial sectors of the temporal

TABLE 4.1 Subdivisions of Memory

Dichotomy	Characteristics
Retrograde	Retrieval of knowledge acquired previously, especially knowledge acquired before the onset of brain injury
Anterograde	Learning of new knowledge, especially learning of knowledge after the onset of brain injury
Verbal	Words, names, verbally coded facts; word-based material
Nonverbal	Faces, geographic routes, complex melodies; spatially based material
Declarative	Information that can be brought into consciousness, "declared," held in the "mind's eye"
Nondeclarative	Performance-based, motor output, habits and conditioning, automatic tendencies
Short-term	Ephemeral (30–45 s), limited capacity (7 ± 2 words, numbers)
Long-term	Permanent, unlimited capacity

TABLE 4.2 Hemispheric Specialization of Memory Systems

Left	Right
Verbal	Nonverbal
Words	Patterns
Names	Faces
Stories	Geographic routes
Lyrics	Complex melodies
Sequential, feature-based	Holistic, gestalt-based
Lexical retrieval	Unique personal knowledge

lobe, including the polar region (Brodmann's area 38), the inferotemporal region (including Brodmann's areas 20, 21, and 36), and the occipitotemporal region (including Brodmann's area 37 and the ventral parts of areas 18 and 19). Autobiographical memory, a special form of retrograde memory that refers to knowledge about one's own past, is linked primarily to the anterior part of the nonmesial temporal lobes, especially in the right hemisphere.

B. Verbal and nonverbal memory. Knowledge can be divided into that which exists in **verbal** form, such as words (written or spoken) and names, and that which exists in **nonverbal** form, such as faces, geographic routes, and complex musical patterns. This distinction is important because memory systems in the two hemispheres of the human brain are specialized differently for verbal and nonverbal material (Table 4.2). Specifically, systems in the left hemisphere are dedicated primarily to verbal material, and systems in the right hemisphere are dedicated primarily to nonverbal material. This arrangement parallels the general arrangement of the human brain, in which the left hemisphere is specialized for language and the right hemisphere for visuospatial processing. This distinction applies to almost all right-handed persons and to approximately two-thirds of left-handed persons. (In the remaining minority of left-handers, the arrangement may be partially or completely reversed.)

C. Declarative and nondeclarative memory.

1. **Declarative memory** (also known as **explicit memory**) refers to knowledge that can be "declared" and brought to mind for conscious inspection, such as facts, words, names, and individual faces, which can be retrieved from memory, placed in the "mind's eye," and reported. The acquisition of declarative memories is intimately linked to the functioning of the hippocampus and other mesial temporal lobe structures.
2. **Nondeclarative memory** (also known as **implicit memory**) refers to various forms of memory that cannot be declared or brought into the mind's eye. Examples include sensorimotor skill learning, autonomic conditioning, and certain types of habits. Nondeclarative memory requires participation of the neostriatum, cerebellum, and sensorimotor cortices. A remarkable dissociation between declarative and nondeclarative learning and memory has been repeatedly found among patients with amnesia (including those with Korsakoff's syndrome, bilateral mesial temporal lobe lesions, medial thalamic lesions, and AD). Among such persons, sensorimotor skill learning and memory often are preserved, whereas declarative memory is profoundly impaired.

D. Short-term and long-term memory.

1. The term **short-term memory** is used to designate a time span of memory that covers from 0 to approximately 45 seconds, a brief period during which a limited amount of information can be held without rehearsal. Also known as primary memory, it does not depend on the hippocampus or other temporal lobe memory systems but is linked closely to cerebral mechanisms required for attention and concentration, such as subcortical frontal structures.
2. The term **long-term memory** refers to a large expanse of time that covers everything beyond short-term memory. Also known as secondary memory, it can be divided into recent (the past few weeks or months) and **remote** (years or decades ago). Unlike short-term memory, the capacity of long-term memory is enormous, and information can be retained in long-term memory almost indefinitely. The mesial temporal system,

including the hippocampus, is required for the acquisition of knowledge into long-term memory. Other systems in the temporal lobe and elsewhere are required for the consolidation and retrieval of knowledge from long-term memory.

E. Working memory refers to a short time during which the brain can hold several pieces of information actively and perform operations on them. It is akin to short-term memory but implies a somewhat longer duration (several minutes) and more focus on the **operational** features of the mental process rather than simply the acquisition of information. It can be thought of as "online" processing and operating on knowledge that is being held in activated form.

Working memory depends on the integrity of the frontal lobes. More specifically, recent functional imaging studies have linked working memory to the dorsolateral prefrontal sector of the frontal lobes. A laterality effect also has been noted wherein verbal working memory tasks depend on the left dorsolateral prefrontal sector, whereas spatial tasks depend on the right dorsolateral prefrontal sector.

II. CLINICAL MANIFESTATIONS

Several frequent neurologic conditions damage memory-related neural systems and lead to various profiles and severities of amnesia (Table 4.3).

A. Degenerative diseases.

1. Cortical dementia.

a. **AD** is characterized by two principal features—the neurofibrillary tangle and the neuritic plaque. Early in the course of the disease, the entorhinal cortex, which is a pivotal way station for input to and from the hippocampus, is disrupted by neurofibrillary tangles in cortical layers II and IV. The perforant pathway, which is the main route for entry into the hippocampal formation, is gradually and massively demyelinated. The hippocampus eventually is almost deafferentated from cortical input. AD also breaks down the efferent linkage of the hippocampus back to the cerebral cortex through destruction of the subiculum and entorhinal cortex. The hallmark behavioral sign of this destruction is amnesia—specifically, an anterograde (learning) defect that covers declarative knowledge but largely spares nondeclarative learning and retrieval. Early in the course of the disease, retrograde memory is relatively spared, but as the pathologic process extends to nonmesial temporal sectors, a defect in the retrograde compartment (retrieval impairment) appears and gradually worsens.

b. **Pick's disease,** characterized by Pick bodies (cells containing degraded protein material), is an uncommon form of cortical dementia that often shows a striking predilection for one lobe of the brain, producing a state of circumscribed lobar atrophy. The disease often is concentrated in the frontal lobes, in which case personality alterations as well as compromised judgment and problem solving, rather than amnesia, are the prominent manifestations. However, the disease can affect one or the other temporal lobe and produce signs of a material-specific amnesia.

TABLE 4.3 Causes of and Conditions Associated with Amnesia

Degenerative disease (e.g., Alzheimer's, Pick's and Parkinson's)
Head injury
Cerebrovascular event (e.g., infarction and ruptured aneurysm)
Toxic conditions (e.g., alcoholism)
Anoxia, ischemia
Herpes simplex encephalitis (HSE)
Surgical ablation
Neoplasm
Normal pressure hydrocephalus
Transient global amnesia (TGA)
Functional amnesia

c. **Frontal lobe dementia** is another form of cortical dementia. It involves focal atrophy of the frontal lobes, which causes personality changes and other signs of executive dysfunction. This condition is similar to Pick's disease, except there is no predominance of Pick bodies.

d. **Frontotemporal dementia** is characterized by symmetric atrophy of the frontal and temporal lobes. The earliest and most prominent cognitive symptoms involve personality and behavioral changes. Although reports of memory problems are common in frontotemporal dementia, they are never the sole or dominating feature. Severe amnesia is considered an exclusionary criterion. Memory functioning is described as selective (e.g., "she remembers what she wants to remember"). Knowledge regarding orientation and current autobiographical events remains largely preserved.

2. **Subcortical dementia.**

a. **Parkinson's disease** is focused in subcortical structures and influences memory in a manner different from cortical forms of dementia such as AD and Pick's disease. Disorders of nondeclarative memory (e.g., acquisition and retrieval of motor skills) are more prominent, and there may be minimal or no impairment in learning of declarative material. Patients with Parkinson's disease often have more problems in **recall** of newly acquired knowledge than in **storage**. When cuing strategies are provided, the patients have normal levels of retention.

b. **Huntington's disease** is also concentrated in subcortical structures and amnesia of patients with Huntington's disease resembles that of patients with Parkinson's disease. In particular, there is disproportionate involvement of nondeclarative memory. Patients with Huntington's disease also tend to have disruption of **working memory**.

c. **Progressive supranuclear palsy** is another primarily subcortical disease process that frequently produces problems with memory. In general, however, the associated amnesia is considerably less severe than that of AD. Laboratory assessment often shows relatively mild defects in learning and retrieval despite the patient's reports of forgetfulness.

3. **Other degenerative conditions.**

a. **Dementia related to Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS)** is notable for varying degrees of memory impairment, with severity being roughly proportional to disease progression. Early in the course, memory defects may be the sole signs of cognitive dysfunction. The problems center on the acquisition of new material, particularly material of the declarative type. Memory defects in this disease appear to be attributable mainly to defective attention, concentration, and overall efficiency of cognitive functioning rather than to focal dysfunction of memory-related neural systems. Various investigators have found that the rate of percentage of CD4 lymphocyte cell loss is associated with and may represent a risk factor for cognitive dysfunction among persons with HIV/AIDS.

b. **Multiple sclerosis (MS)** patients have varying degrees of amnesia, although the severity can wax and wane considerably in concert with other neurologic symptoms. Many patients with MS have no memory defects during some periods of the disease. When present, the memory impairment most commonly manifests as defective recall of newly learned information. Encoding and working memory are normal or near-normal. Patients with MS often benefit from cuing. The amnesia of MS usually affects declarative material of both verbal and nonverbal types; defects in nondeclarative memory are rare.

B. Head injury. Several distinct types of amnesia are associated with head injury.

1. **Post-traumatic amnesia** refers to the period of time following head trauma during which patients do not acquire new information in a normal and continuous manner despite being conscious. During this time, the patient may appear alert and attentive and may even deny having memory problems. It becomes apparent later that the patient was not forming ongoing records of new experiences. Information is not encoded, and no amount of cuing will uncover memories that would normally have been acquired during this period. The **duration** of post-traumatic amnesia is a reliable marker of the severity of head injury and constitutes one of the best predictors of outcome.

2. **Retrograde amnesia** is the defective recall of experiences that occurred immediately before the head injury. Information from the time closest to the point of injury is most likely to be lost. The extent of retrograde amnesia typically "shrinks" as the patient recovers, and patients are typically left with only a small island of amnesia for the few minutes or hours immediately before the trauma.
3. **Learning defects (anterograde amnesia)** can occur in moderate and severe head injuries when there is permanent damage to mesial temporal lobe structures, such as the hippocampus. The impairment is centered on declarative knowledge; nondeclarative learning is rarely affected. The defect may be unequal for verbal and nonverbal material if there is asymmetry of the structural injury.

C. Cerebrovascular disease.

1. **Stroke** is a frequent cause of amnesia, and the nature and degree of memory disturbance are direct functions of which neural structures are damaged and to what extent. Amnesia is most likely to result from infarction that damages the mesial temporal region, the basal forebrain, or the medial diencephalon, especially the thalamus.
   a. In the **mesial temporal lobe,** the parahippocampal gyrus and hippocampus proper can be damaged by infarction in territories supplied by branches of the middle cerebral or posterior cerebral arteries. (Strokes in the region of the anterolateral temporal lobe are uncommon.) Infarction of this type almost always is unilateral and almost always produces incomplete damage to mesial temporal memory structures; hence, the profile is one of a partial material-specific defect in anterograde memory for declarative knowledge.
   b. The most severe memory impairment results from bilateral infarcts situated in the anterior part of the **thalamus** in the interpeduncular profundus territory. Unilateral lesions caused by lacunar infarction in anterior thalamic nuclei produce material-specific learning defects reminiscent of those observed with mesial temporal lobe lesions. Patients with thalamic damage, however, tend to have both anterograde and retrograde defects. In the retrograde compartment, a **temporal gradient** to the defect is common—that is, the farther back in time one goes, the less the severity of the amnesia.
2. **Ruptured aneurysms** located either in the anterior communicating artery or in the anterior cerebral artery almost invariably causes infarction in the region of the basal forebrain—a set of bilateral paramidline gray nuclei that includes the septal nuclei, the diagonal band of Broca, and the substantia innominata. The amnesia associated with basal forebrain damage has several distinctive features. Patients have an inability to link correctly various aspects of memory episodes (when, where, what, and why). This problem affects both the anterograde and retrograde compartments. Confabulation is common among patients with basal forebrain amnesia. Cuing markedly improves recall and recognition of both anterograde and retrograde material.
3. **Vascular dementia** (VaD) refers to conditions in which repeated infarction produces widespread cognitive impairment, including amnesia. The term is used most commonly to denote multiple small strokes (lacunar strokes) in the arterioles that feed subcortical structures; hence, the usual picture is "subcortical" dementia. The memory impairment in VaD generally affects encoding of new material (anterograde amnesia), and nondeclarative learning also may be defective. Retrograde memory tends to be spared.

D. Toxic conditions.

1. **Alcoholism** can produce permanent damage to certain diencephalic structures, particularly the mammillary bodies and dorsomedial thalamic nucleus, which have been linked to amnesic manifestations. This presentation is known as **alcoholic Korsakoff's syndrome** or **Wernicke–Korsakoff's syndrome**. The amnesic profile in patients with Korsakoff's syndrome is characterized by (1) anterograde amnesia for both verbal and nonverbal material with defects in both encoding and retrieval, (2) retrograde amnesia with a strong temporal gradient—that is, progressively milder defects as one goes farther back in time, and (3) sparing of nondeclarative memory. Confabulation is characteristic of patients with Korsakoff's syndrome, especially in the early days following detoxification.
2. **Other neurotoxins** such as metals, especially lead and mercury, solvents and fuels, and pesticides, can cause amnesia from acute or chronic exposure. The relation between exposure to these substances and cognitive dysfunction is poorly understood, but there

is little doubt that memory impairment often does result from excessive exposure to these neurotoxins. The amnesia tends to manifest as a deficiency in new learning (anterograde amnesia) that covers various types of material, including verbal, nonverbal, and nondeclarative. Defects of concentration, attention, and overall cognitive efficiency are frequent contributing factors. In most cases, the memory impairment occurs in the setting of more widespread cognitive dysfunction.

E. **Anoxia/ischemia**, which frequently occurs in the setting of cardiopulmonary arrest, often leads to the selective destruction of cellular groups within the hippocampal formation. The extent of damage is linked to the number of minutes of arrest. Brief periods of anoxia/ischemia can cause limited damage, and longer periods produce greater destruction. With a critical length of deprivation, the damage concentrates bilaterally in the CA1 ammonic fields of the hippocampus. The result is selective anterograde amnesia affecting declarative verbal and nonverbal material. The amnesia associated with anoxia/ischemia is reminiscent of the memory defect produced by early-stage AD.

F. **Herpes simplex encephalitis** (HSE) causes a severe necrotic process in the cortical structures associated with the limbic system, some neocortical structures in the vicinity of the limbic system, and several subcortical limbic structures. The parahippocampal gyrus—particularly the entorhinal cortex in its anterior sector and the polar limbic cortex (Brodmann's area 38)—is frequently damaged. HSE also may destroy neocortices of the anterolateral and anteroinferior regions of the temporal lobe (Brodmann's areas 20, 21, anterior 22, and parts of 36 and 37). The destruction may be bilateral, but with the advent of early diagnosis and treatment, circumscribed unilateral damage has become more common. The profile of amnesia caused by HSE is dictated by the nature of neural destruction. Damage confined to the mesial temporal region produce anterograde declarative memory impairment. When HSE-related pathologic changes extend to nonmesial temporal structures in anterolateral and anteroinferior sectors, the amnesia involves progressively greater portions of the retrograde compartment. The retrograde defect can be quite severe if nonmesial temporal structures are extensively damaged and, in the worst case, a patient can lose almost all capacity to remember declarative information from the past and are not able to learn new information (**global amnesia**).

G. **Surgical ablation** of intractable epilepsy, especially temporal lobectomy, can result in memory impairment. Even if the resection spares most of the hippocampus proper, the resection usually involves other anterior regions of the mesial temporal lobe, including the amygdala and entorhinal cortex, resulting in mild but significant memory defects. In the most common presentation, the patient has a material-specific learning defect (nonverbal if the resection is on the right, verbal if it is on the left) after temporal lobectomy. In addition, the amnesia affects only declarative knowledge. However, mild retrograde amnesia can also result if there is sufficient involvement of the anterolateral and anteroinferior temporal sectors. Generally speaking, patients whose seizures began at an early age are less affected by temporal lobectomy than are patients whose seizures began later.

H. **Neoplasms** can lead to amnesia, depending on their type and location. Impaired memory is a common symptom of brain tumors, especially those centered in the region of the third ventricle (in or near the thalamus) or in the region of the ventral frontal lobes (in or near the basal forebrain). The most common therapies for high-grade malignant brain tumors, including resection and radiation, often produce memory defects. Radiation necrosis, for example, can damage the lateral portions of the temporal lobes and lead to a focal retrograde amnesia.

I. **Normal pressure hydrocephalus** is a partially reversible condition in which gait disturbance, incontinence, and dementia, especially memory impairment, compose a hallmark triad of presenting features. Early in the course, memory impairment can be minimal, but most patients with normal pressure hydrocephalus go on to have marked memory defects. The typical situation is anterograde amnesia for declarative material; however, problems with attention and concentration can exacerbate the amnesia and make the patient appear even more impaired than he or she actually is.

J. **Transient global amnesia** (TGA) is a short-lasting neurologic condition in which the patient has prominent impairment of memory in the setting of otherwise normal

cognition and no other neurologic defect. The duration of TGA typically is approximately 6 or 7 hours, after which the condition spontaneously remits, and the patient returns to an entirely normal memory status. The cause of TGA is unknown, although psychological stress, vascular factors, seizure, and migraine have all been proposed as causes. During the episode, the patient has severe impairment of anterograde memory for verbal and nonverbal material. Retrograde memory is impaired to a lesser degree. After recovery, patients are unable to remember events that transpired during the episode, and sometimes a short period of time immediately before the onset of TGA also is lost. Otherwise, there is no long-term consequence.

K. Functional amnesia can occur in the absence of any demonstrable brain injury, as a consequence of severe emotional trauma, hypnotic suggestion, or psychiatric illness. These presentations have been called *functional amnesia* to differentiate them from amnesia caused by "organic" factors, although at the molecular and cellular levels the mechanisms may not be distinguishable. A common form is **functional retrograde amnesia**, in which the patient loses most or all memory of the past (including self-identity), usually after a severe emotional or psychological trauma. Curiously, anterograde memory can be entirely normal, and the patient may even have "relearning" of the past. Spontaneous recovery is frequent, although most patients are never able to remember events that transpired during the episodes in which they had amnesia. Another interesting form is **posthypnotic amnesia**, the phenomenon whereby patients cannot remember events that transpired while they were under hypnosis.

III. EVALUATION

A. History.

1. **Onset.** Through careful history taking, the clinician should determine as precisely as possible the timing of the **onset** of the problem. Memory defects that began years ago and have gradually worsened over time point to degenerative disease, such as AD. Reports of sudden memory impairment among younger patients, for whom psychological factors (e.g., severe stress and depression) can be identified as being temporally related to the problem, should raise the question of nonorganic etiologic factors.
2. **Course.** The history taking should document carefully the **course** of the concern. Progressive deterioration in memory signals a degenerative process. Memory defects after head injury or cerebral anoxia, by contrast, tend to resolve gradually, and reports to the contrary raise the question of other (psychological) factors.
3. **Nature.** The clinician should explore the **nature** of the problem. With what types of information, and in what situations, is the patient having trouble? Patients may produce vague, poorly specified concerns (e.g., "My memory is bad" or "I'm forgetful"), and it is important to request specific examples to form an idea as to the actual nature of the problem. Patients tend to use the term "memory impairment" to cover a wide range of mental status abnormalities, and, again, elicitation of examples is informative. Patients who say they "can't remember" may actually have circumscribed impairment of word finding, proper name retrieval, or hearing or vision.

B. Bedside examination. Memory assessment is covered to some extent by almost all bedside or screening mental status examinations. If patients pass such examinations, do not report memory impairment, and are not described by spouses or caretakers as having memory difficulties, it is safe to assume that memory is normal. If any of these conditions are not met, a more complete evaluation of memory is warranted. Referral for neuropsychological assessment provides the most direct access to such evaluation.

1. **Learning.** Can the patient learn the examiner's name? Three words? Three objects?
2. **Working memory.** Backward spelling, serial subtraction, and repeating numerical strings of digits backward are good probes of working memory.
3. **Delayed recall.** It is important to ask for the retrieval of newly acquired knowledge after a delay, for example, approximately 30 minutes. This may reveal a severe loss of information on the part of a patient who performed perfectly in an immediate recall procedure.

4. **Retrograde memory.** The patient should be asked to retrieve knowledge from the past. This should be corroborated by a spouse or other **collateral person**, because patients with memory defects may confabulate and otherwise mislead the examiner.
5. **Orientation.** The patient should be asked for information about time, place, and personal facts. Defects in orientation often are early clues to memory impairment.
6. **Attention.** Marked impairment of attention produces subsequent defects on most tests of memory. The diagnosis of amnesia, however, should be reserved for patients who have normal attention but still cannot perform normally on memory tests. Attentional impairment per se is a hallmark of other abnormalities, not necessarily of an amnesic condition.

C. **Laboratory studies** of memory are conducted in the context of neuropsychological assessment, which provides precise, standardized quantification of various memory capacities. Examples of some widely used procedures are as follows.

1. **Anterograde memory.** Most conventional neuropsychological tests of memory, including the Wechsler Memory Scale, fourth edition (WMS-IV), and other such instruments, assess **learning of declarative knowledge**. It should not be assumed that all aspects of memory are normal simply because the patient passes these procedures. For example, these tests do not measure nondeclarative memory, and they rarely provide adequate investigation of the retrograde compartment. Nonetheless, the WMS-IV and related procedures provide sensitive, standardized means of quantifying many aspects of memory.
   a. **Verbal.** In addition to several verbal memory procedures that comprise part of the WMS-IV (e.g., paragraph recall and paired-associate learning), there are several well-standardized list-learning procedures in which the patient attempts to learn and remember a list of words. The Rey Auditory-Verbal Learning Test, for example, requires the patient to learn a list of 15 words. Five successive trials are administered, and then a delayed recall procedure is performed after about 30 minutes. The patient's learning capacity, learning curve, and the degree of forgetting can be determined.
   b. **Nonverbal memory tests** typically involve administration of various designs, such as geometric figures, that the patient must remember (e.g., WMS-IV Visual Reproduction and the Benton Visual Retention Test). Face-learning procedures also provide good tests of nonverbal memory.
2. **Retrograde memory.** There are several standardized procedures for measuring retrograde memory, including the Remote Memory Battery, the Famous Events Test, and the Autobiographical Memory Questionnaire. These procedures probe recall and recognition of various historical facts, famous events and persons, and autobiographical knowledge. Corroboration of retrograde memory, particularly with regard to autobiographical information, is extremely important to determine the severity of retrograde memory defects.
3. **Nondeclarative memory.** A standard procedure for measuring non-declarative learning is the Rotary Pursuit Task which requires the patient to hold a stylus in one hand and attempt to maintain contact between the stylus and a small metal target while the target is rotating on a platter. Successive trials are administered and are followed by a delay trial. This procedure allows the measurement of acquisition and retention of the motor skill.
4. **Working memory.** The Digit Span Backward and Sequencing Subtests from the WAIS-IV provide a sensitive means of quantifying working memory. The Trail-Making Test, which requires the patient to execute a psychomotor response while tracking dual lines of information, is also a good probe of working memory. Another commonly used procedure is the Paced Auditory Serial Addition Test, in which the patient must add numbers in an unusual format under increasingly demanding time constraints. Finally, two subtests from a previous version of the Wechsler Memory Scale (WMS-III), Spatial Span and Letter-Number Sequencing, together create a working memory index. Spatial Span is the visual–spatial analog of the aforementioned auditory–verbal subtest, Digit Span. Rather than recalling numbers in forward and backward order, spatial span requires the examinee to replicate, forward and backward, an increasingly long series of visually presented spatial locations. In Letter–Number Sequencing, the patient is read a combination of numbers and letters of varying lengths and is asked to repeat them by first stating the numbers in ascending order and then the letters in alphabetical order.
5. **Long-term memory.** The ability to acquire new information, in addition to consolidate and store that information and retrieve it at a later time, is the real crux of memory. In a practical sense, it is not very helpful to have normal short-term memory if one cannot

transfer the information into a more permanent storage area. Hence, delayed recall and recognition procedures, which yield information about the status of long-term memory, are very important in memory assessment.

IV. DIFFERENTIAL DIAGNOSIS

Different causes of amnesia have different implications for diagnosis and management. The following common differential diagnoses are particularly challenging.

A. Normal aging. A seemingly minor but practically difficult challenge is to differentiate true memory impairment from the influences of normal aging. Aging produces certain declines in memory, which can be misinterpreted by patients and clinicians alike as signs of neurologic disease. Many elderly persons who report "forgetfulness" turn out to have peer-equivalent performances on all manner of standard memory tests, and the diagnosis of amnesia is not applicable. Patients may be quick to interpret any episode of memory failure as a sign of AD, or they may adamantly deny memory dysfunction in the face of obvious real-world impairment. Consequently, careful quantification of the memory profile aids in the differential diagnosis.

B. Psychiatric disease. Many psychiatric diseases produce some degree of memory impairment. Accurate diagnosis is critical, because most memory defects caused by psychiatric disease are reversible, unlike most of amnesia that occurs in the setting of neurologic disease.

1. **Pseudodementia** is a condition that produces memory impairment and other cognitive defects resembling "dementia" but not caused by neurologic disease. Severe depression is the typical cause. Patients with pseudodementia often have memory impairment such as anterograde amnesia that is quite similar to that in the early stages of degenerative dementia. However, depressed patients respond to treatment with antidepressant medications and psychotherapy; when the affective disorder lifts, memory returns to normal.
2. **Depression** is a common cause of memory impairment among all age groups. Distinguishing features, however, help differentiate amnesia due to depression from amnesia caused by neurologic disease. Depressed patients tend to have problems in concentration and attention, and they may have defects in working memory and other short-term memory tasks. Long-term memory is less affected, and retrograde memory is normal. Apathetic, "don't know" responses are common among depressed patients, whereas patients with a neurologic disorder more often give incorrect, off-target responses. Depressed patients also tend to describe their memory problems in great detail, whereas patients with a neurologic disorder, such as those with suspected Alzheimer's dementia, generally discount memory problems. Patient history is informative and the clinician usually can find evidence of major stress, catastrophe, or other circumstances, and it is apparent that the onset of the memory problems coincided with the onset of the affective disorder.

C. Side effects of medications. Many medications commonly prescribed for older adults produce adverse side effects on cognitive function, including memory. It is important to know what medications a patient has been taking and to account for the extent to which those medications may be causing memory impairment. The history often reveals that the onset of memory problems coincided with or soon followed the beginning of use of a particular medication. Memory defects caused by medication side effects also tend to be variable—for example, worse at certain times of the day. The main problems concern attention, concentration, and overall cognitive efficiency; memory defects are secondary.

V. DIAGNOSTIC APPROACH

The diagnostic approach to a patient with amnesia should include any procedures necessary for establishing both the most likely **cause** and the precise **nature** of the memory impairment. The most commonly used procedures are as follows.

A. **Neurologic examination** should establish whether a memory problem is present, the general degree of severity, and the history of the problem. It is not uncommon for patients with amnesia to underestimate or even deny the problem; information from a spouse or caretaker is a critical part of the history. Careful mental status testing can provide sufficient characterization of the amnesia profile.

B. **Neuroimaging procedures,** including MRI and CT, almost always are helpful in diagnosing the cause of amnesia. Functional imaging, such as positron emission tomography, may demonstrate abnormalities suggestive of AD (e.g., bilateral parietotemporal hypometabolism) earlier in the natural course of the disease than may MRI, CT, or clinical assessment.

C. **Neuropsychological assessment** provides detailed quantification of the nature and extent of memory impairment. Such testing should be considered for almost all patients with amnesia, although there may be instances in which the mental-status-testing portion of the neurologic examination provides sufficient information.

VI. CRITERIA FOR DIAGNOSIS

The diagnosis of amnesia is appropriate whenever there are memory defects that exceed those expected given the patient's age and background. Some conditions, such as severe aphasia, make it difficult to assess memory in a meaningful way. Amnesia should not be diagnosed if the patient is in a severe confusional state, in which attentional impairment rather than memory dysfunction is the principal manifestation. Otherwise, amnesia can occur in isolation or coexist with almost any other form of impairment of mental status. It is customary to regard patients as having **amnesia** if there is considerable discrepancy between the level of intellectual function and one or more memory functions. There are many different subtypes of amnesia. Diagnosis of such subtypes usually requires fine-grained quantification, such as that provided in a neuropsychological laboratory.

VII. REFERRAL

A. **Neuropsychological** evaluation is appropriate for almost all patients with manifestations of amnesia. The following situations that occur commonly in clinical practice particularly call for such a referral.

1. **Precise characterization of memory capacities.** For a patient who has sustained brain injury, neuropsychological assessment provides detailed information regarding the strengths and weaknesses of the patient's memory. In most instances, memory assessment should be performed as early as possible in the recovery period. This evaluation provides a baseline to which recovery can be compared. Follow-up assessments assist in monitoring recovery, determining the effects of therapy, and making long-range decisions regarding educational and vocational rehabilitation.
2. **Monitoring the status of patients who have undergone medical or surgical intervention.** Serial neuropsychological assessment of memory is used to track the course of patients who are undergoing medical or surgical treatment for neurologic disease. Typical examples include drug treatment for patients with Parkinson's disease, seizure disorder, surgical intervention for patients with normal pressure hydrocephalus, or a brain tumor. Neuropsychological assessment provides a baseline memory profile with which changes can be compared and provides a sensitive means of monitoring changes in memory that occur in relation to particular treatment regimens.
3. **Differentiating "organic" from psychiatric disease.** Neuropsychological assessment can provide evidence crucial to the distinction between amnesic conditions that are primarily or exclusively "organic" and those that are primarily or exclusively "psychiatric." A common diagnostic dilemma faced by neurologists and psychiatrists is differentiating "true dementia" (e.g., cognitive impairment caused by AD) and "pseudodementia" (e.g., cognitive impairment associated with depression).

4. **Medicolegal situations.** Cases in which "brain injury" and "memory impairment" are claimed as damages by plaintiffs who allegedly have sustained minor head injuries or have been exposed to toxic chemicals. In particular, there are many cases in which hard or objective signs of brain dysfunction (e.g., weakness, sensory loss and impaired balance) are absent, neuroimaging and EEG findings are normal, and the entire case rests on claims of cognitive deficiencies, particularly memory dysfunction. Neuropsychological assessment is crucial to the evaluation of such claims.
5. **Conditions in which known or suspected neurologic disease is not detected with conventional neurodiagnostic procedures.** There are situations in which the findings of standard diagnostic procedures, including neurologic examination, neuroimaging, and EEG, are equivocal, even though the history indicates that brain disease and amnesia are likely. Examples include mild closed head injury, the early stages of degenerative demential syndromes, and early HIV-related dementia. Neuropsychological assessment in such cases provides the most sensitive means of evaluating memory.
6. **Monitoring changes in cognitive function over time.** In degenerative dementia in particular, equivocal findings in the initial diagnostic evaluation are not uncommon. In such cases, follow-up neuropsychological evaluation can provide important confirming or disconfirming evidence regarding the status of the patient's memory.

B. **Rehabilitation.** Another common application of neuropsychological assessment is the case in which a patient undergoes cognitive rehabilitation for amnesia. Neuropsychological data collected at the initial assessment can help determine how to orient the rehabilitation effort. Subsequent examinations can be used to measure progress during therapy.

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Recommended Readings

Adolphs R, Tranel D, Denburg NL. Impaired emotional declarative memory following unilateral amygdala damage. *Learn Mem*. 2000;7:180–186.

Alexander MP. Mild traumatic brain injury: pathophysiology, natural history, and clinical management. *Neurology*. 1995;45:1253–1260.

Bachevalier J, Meunier M. Cerebral ischemia: are the memory deficits associated with hippocampal memory loss? *Hippocampus*. 1996;6:553–560.

Baddeley AD. Working memory. *Science*. 1992;255:566–569.

Cabeza R, Nyberg L. Imaging cognition, II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci*. 2000;12:1–47.

Cohen NJ, Squire LR. Preserved learning and retention of pattern-analyzing skill in amnesia: dissociation of knowing how and knowing that. *Science*. 1980;210:207–210.

Corkin S. Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H.M. *Semin Neurol*. 1984;4:249–259.

Damasio AR. Time-locked multiregional retroactivation: a systems-level proposal for the neural substrates of recall and recognition. *Cognition*. 1989;33:25–62.

Hannula DE, Tranel D, Cohen N. The long and the short of it: relational memory impairments in amnesia, even at short lags. *J Neurosci*. 2006;26:8352–8359.

Heindel WC, Salmon DP, Shults CW, et al. Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's and Parkinson's disease patients. *J Neurosci*. 1989;9:582–587.

Hyman BT, Kromer LJ, Van Hoesen GW. A direct demonstration of the perforant pathway terminal zone in Alzheimer's disease using the monoclonal antibody Alz-50. *Brain Res*. 1988;450:392–397.

Kroll NE, Markowitsch HJ, Knight RT, et al. Retrieval of old memories: the temporofrontal hypothesis. *Brain*. 1997;120:1377–1399.

Markowitsch HJ. Which brain regions are critically involved in the retrieval of old episodic memory? *Brain Res Rev*. 1995;21:117–127.

Milner B, Squire LR, Kandel ER. Cognitive neuroscience and the study of memory. *Neuron*. 1998;20:445–468.

Silverman DH, Truong CT, Kim SK, et al. Prognostic value of regional cerebral metabolism in patients undergoing dementia evaluation: comparison to a quantifying parameter of subsequent cognitive performance and to prognostic assessment without PET. *Mol Genet Metab*. 2003;80(3):350–355.

Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol Rev*. 1992;99:195–231.

Tranel D, Damasio AR. The covert learning of affective valence does not require structures in hippocampal system or amygdala. *J Cogn Neurosci*. 1993;5:79–88.

Tranel D, Damasio AR, Damasio H, et al. Sensorimotor skill learning in amnesia: additional evidence for the neural basis of nondeclarative memory. *Learn Mem*. 1994;1:165–179.

Tranel D, Damasio H, Damasio AR. Amnesia caused by herpes simplex encephalitis, infarctions in basal forebrain, and anoxia/ischemia. In: Boller F, Grafman J, eds. *Handbook of Neuropsychology*. 2nd ed. Amsterdam, The Netherlands: Elsevier Science; 2000:85–110.

Van Hoesen GW. The parahippocampal gyrus. *Trends Neurosci*. 1982;5:345–350.

CHAPTER 5

Approach to the Comatose Patient

Michael P. Merchut

Interpersonal communication and cognitive behavior require sufficient wakefulness, arousal, or alertness. Patients in the persistent vegetative state appear conscious or awake at times, but have little to no communicative or cognitive ability. **Coma** is the unconscious, sleep-like state of patients who are unresponsive to stimuli. Coma may be due to severe, even lethal, brain damage, or to potentially treatable or reversible causes. Comatose patients thus require prompt evaluation, followed by appropriate therapeutic intervention.

Arousal is a function of the **ascending reticular activating system (ARAS)**, a complex pathway from pons to midbrain to intralaminar thalamic nuclei and basal forebrain, with diffuse cortical connections. Single structural lesions, such as an ischemic infarct or tumor, may produce coma by directly disrupting this pathway in the upper brainstem. However, a unilateral cerebral hemispheral lesion does not produce coma unless it creates enough edema and midline shift to adversely affect the ARAS bilaterally, typically at the thalamic level. Coma may also occur from extensive, severe, bilateral cortical lesions, such as multiple hemorrhages, or from metabolic processes suppressing cortical function in a global way, such as drug intoxication or hypoglycemia. If treated immediately, hypoglycemic coma may resolve completely, as may other toximetabolic etiologies. Certain causes of coma, such as fulminant encephalitis, are progressively fatal, and the patient never wakens. In other situations, such as anoxic encephalopathy, the patient may "wake up" after several days of coma, yet remain in a persistent vegetative state with poor or no cognitive recovery.

I. EVALUATION

A. History.

1. Sudden onset of coma is suggestive of the following:
   a. Intracranial hemorrhage (prodromal severe headache may accompany subarachnoid hemorrhage [SAH] from a ruptured intracranial aneurysm, or occur with cerebral hemorrhage).
   b. Critical brainstem infarction or multiple embolic cerebral infarcts.
   c. Significant cerebral hypoperfusion after cardiopulmonary arrest.
   d. Observed or unwitnessed head trauma.
2. Confusion or delirium preceding coma is suggestive of a toximetabolic etiology (organ dysfunction or infection, electrolyte disorder, medicinal or drug toxicity).
3. Important information to obtain immediately consists of the following:
   a. Current medications, especially any diabetic, anticonvulsant, cardiac drugs, or warfarin.
   b. Any history of adverse or allergic medicinal reactions.
   c. Any history of recent head trauma, febrile or other illness, or previous neurological symptoms.
   d. Any use of recreational drugs.

B. Physical examination.

1. A rapid **general or systemic examination** may provide important clues for the etiology of coma.
   a. **Hypertension** to an extreme degree may point to causes other than an acute cerebral hemorrhage or infarction, including hypertensive encephalopathy, cocaine abuse, or eclampsia.
   b. **Hypotension** reflects hypovolemia, cardiogenic or septic shock.
   c. **Fever** accompanies systemic or CNS infections, as well as malignant hyperthermia, neuroleptic malignant syndrome, or serotonin syndrome.
   d. **Hypothermia** after cold exposure may even mimic brain death.

e. **Cutaneous bleeding** around the eyes or mastoid area accompanies skull fractures. More diffuse hematomas suggest a systemic bleeding disorder. Infective endocarditis may cause "splinter" nailbed or palmar/plantar hemorrhages, producing coma by means of cerebral infarcts or abscesses.
f. **Jaundice and ascites** may be noted in hepatic coma patients, as well as hepatosplenomegaly.
g. An **arrhythmia or heart murmur** may be clues for cardiogenic shock, cerebral cardioemboli, or infective endocarditis.
h. Once cervical spine stability is assured, the finding of **nuchal rigidity** suggests infective meningitis or SAH, but may disappear in deeper stages of coma.
i. **Papilledema** evolves a few hours after severe elevation in intracranial pressure. The funduscopic examination may also reveal preretinal "fluid level" hemorrhages from subarachnoid bleeding or retinal hemorrhages from infective endocarditis.

C. Although the **neurological examination** in coma is limited, it offers not only a means of localizing the level of neurological deficit, but also serves as a serial measurement of improvement or deterioration. Developed initially for use in trauma patients, the **Glasgow Coma Scale** is an easy and reproducible scoring system for all medical personnel, as is the more recently developed **FOUR Score** (see Table 5.1), which also assesses brainstem reflexes and breathing patterns.

1. Motor responsiveness.
a. Record your observations of the verbal and motor responses from the patient, rather than using brief terms (stuporous, obtunded) with variable meaning.
b. Verbal responses include oriented conversation, disoriented communication, meaningless words or sounds, to unresponsiveness.
c. Motor responses include spontaneous limb movements, limb movements on command, limb withdrawal to noxious stimuli, to unresponsiveness.

TABLE 5.1 Coma Scales

Glasgow Coma Scale	Full Outline of UnResponsiveness (FOUR)
Eye response	**Eye response**
4, eyes open spontaneously	4, eyelids open or opened, tracking, or blinking to command
3, eyes open to command	3, eyelids open but not tracking
2, eyes open to pain	2, eyelids closed but open to loud voice
1, no eye opening	1, eyelids closed but open to pain
	0, eyelids remain closed with pain
Motor response	**Motor response**
6, follows commands	4, thumbs up, fist or peace sign
5, localizes pain	3, localizing to pain
4, withdraws from pain (flexion)	2, flexion response to pain
3, decorticate posturing to pain	1, extension response to pain
2, decerebrate posturing to pain	0, no response to pain or generalized myoclonus status
1, no motor response	
	Brainstem reflexes
Verbal response	4, pupil and corneal reflexes present
5, oriented and converses	3, one pupil wide and fixed
4, disoriented and converses	2, pupil or corneal reflexes absent
3, uses inappropriate words	1, pupil and corneal reflexes absent
2, incomprehensible sounds	0, absent pupil, corneal and cough reflex
1, no verbal response	
	Respiration
	4, not intubated, regular breathing pattern
	3, not intubated, Cheyne–Stokes breathing pattern
	2, not intubated, irregular breathing
	1, breathes above ventilator rate
	0, breathes at ventilator rate or apnea

(1) Decorticate posturing (upper limb flexion with lower limb extension, uni- or bilateral) localizes to the cerebral hemispheres or thalamus.
(2) Decerebrate posturing (upper and lower limb extension, uni- or bilateral) localizes to the midbrain (red nucleus).
(3) If required, noxious stimuli include rubbing the sternum, or applying firm but gentle pressure to the forehead or nailbeds.
(4) Asymmetrical limb movements or hypertonia occur with structural brain lesions, whereas symmetrical motor responses are typical with toximetabolic conditions.
(5) Bilateral myoclonic jerks, asterixis, or tremulousness strongly suggest toximetabolic causes of coma.
(6) Asymmetrical or focal, rhythmical movements may be subtle clues when nonconvulsive status epilepticus causes coma.

2. **Respiratory patterns** do not strictly correlate with the level of brain dysfunction as once thought and may be obscured if the patient is mechanically ventilated.
   a. Cheyne–Stokes' breathing is observed as periods of increasing, then decreasing, tidal volumes and respiratory rate, followed by seconds of apnea.
      (1) It occurs more commonly in elderly patients, with or without systemic medical problems or congestive heart failure.
      (2) It may occur from bilateral cerebral lesions or a unilateral lesion with brain shift.
   b. Persistent hyperventilation occurs more often from pulmonary causes like pneumonitis, and rarely from midbrain lesions.
   c. Arrhythmical, irregular respirations accompany dysfunction at the medulla, where critical cardiorespiratory centers are located.
3. **The pupils** are typically small but reactive to light in the elderly, as well as those in toximetabolic coma, where other cranial nerve reflexes may be absent.
   a. A unilaterally large pupil unreactive to light ("fixed or blown pupil") in an unresponsive patient represents dysfunction of third cranial nerve pupilloconstrictive fibers.
      (1) Most commonly found with ipsilateral temporal lobe compression of the third cranial nerve (uncal herniation) from hemorrhage or edema.
      (2) Rarely due to a ruptured intracranial aneurysm at the junction of the internal carotid-posterior communicating artery.
      (3) Asymmetrical pupils reflect a structural cause of coma.
   b. Bilaterally midposition to large, unreactive pupils may occur with midbrain lesions or terminal anoxic brain injury.
   c. Pinpoint, reactive pupils are caused by extensive pontine lesions interrupting the descending sympathetic pupillodilator fibers; however,
      (1) pinpoint pupils can also be caused in older patients by cholinergic eyedrops for glaucoma, and
      (2) narcotic overdose can also produce small pupils.
4. **Ocular reflexes,** when present in a comatose patient, indicate preserved brainstem function in the absence of over-riding cortical control.
   a. The oculocephalic ("doll's eyes") reflex occurs when the examiner passively turns the head to one side, eliciting a normal lateral conjugate rolling of the eyes to the opposite side.
   b. The oculovestibular ("cold caloric") reflex occurs after sequential instillation of 50- to 200-cc ice water into one ear canal, with the head elevated 30°, eliciting a slow, tonic deviation of both eyes toward the irrigated ear, after several seconds delay.
      (1) Ensure that the tympanic membrane is intact, so nonsterile water and debris cannot enter the middle ear.
      (2) Ensure there is no impacted cerumen in the ear canal, causing a false negative test.
      (3) Lateral jerk nystagmus of the eyes toward the nonirrigated ear occurs in conscious patients, but not comatose patients where cortical function is depressed.
   c. Ocular reflexes
      (1) should not be checked in trauma patients until cervical spine stability is assured,
      (2) may be absent because of previous labyrinthine trauma, mastoiditis or toxicity from benzodiazepines or barbiturates, and

(3) appear asymmetrical from a structural lesion affecting the brainstem, or from facial bone fractures restricting extraocular muscle function.

d. In coma,
(1) the eyes are slightly divergent at rest,
(2) conjugate lateral deviation of the eyes toward one side occurs from a lesion in the contralateral brainstem or ipsilateral cerebral hemisphere,
(3) persistent, rhythmical nystagmus may be a subtle finding of nonconvulsive status epilepticus, and
(4) "ocular bobbing" consists of repetitive downward jerks of the eyes, with slower updrift, due to pontine lesions with poor outcome.

e. Blinking
(1) occurs spontaneously if the pontine ARAS is intact and
(2) along with vertical eye movements may be the only motor functions (and means of communication) in a patient with the "locked-in syndrome" from basilar artery occlusion or severe neuromuscular paralysis.

II. ETIOLOGY

A. Toximetabolic coma accounts for almost two-thirds of unresponsive emergency room patients.

1. A confusional state or delirium occurs initially, followed by symmetrical motor or ocular reflex findings and preserved pupillary light reflex.
2. Exceptionally, hemiparesis or aphasia may be due to hyperglycemic, hypoglycemic, hyponatremic, or dysosmolar states.
3. Tremulousness, myoclonic jerks, and asterixis are typical.
4. Drug intoxication or overdose may also lead to subsequent traumatic brain injury and structural lesions leading to coma.

B. Structural coma accounts for about one-third of unresponsive emergency room patients.

1. Asymmetrical motor or ocular reflex findings occur early.
2. A unilaterally dilated pupil unresponsive to light indicates uncal herniation until proven otherwise.

III. DIFFERENTIAL DIAGNOSIS

A. Brain death.

1. Irreversible, severe loss of brain and brainstem function.
   a. Comatose patient with absence of all brainstem reflexes, including spontaneous respiration (abnormal bedside apnea test: no observed breaths despite $pCO_2 \geq 60$ mm, while on 100% oxygen).
   b. The cause of coma is known and sufficient to cause brain death, such as cardiopulmonary arrest.
2. No improvement occurs during observation and treatment.
   a. Observation is at least 6 hours in adults, 12 hours to 2 days for children.
   b. Hypothermia, hypotensive shock, and drug intoxication have been ruled out or treated.
   c. Ancillary testing may help to confirm the clinical diagnosis (absent cerebral blood flow on radioisotope brain scan, or "flat-line" EEG).

B. Persistent vegetative state.

1. After several days of coma, the patient appears intermittently awake, breathes spontaneously, and exhibits primitive reflexes or eye-roving behavior.
2. Severe cerebral damage persists, however, and no meaningful communication or cortical responsiveness occurs.

C. "Locked-in syndrome."

1. The patient may appear to be in a persistent vegetative state, and is unable to move the limbs and face, or gaze laterally ("de-efferented").
2. Vertical gaze and eyeblinking are preserved, and serve as a means of proving that communication and cortical functions are preserved (the patient accurately blinks once for "yes," or twice for "no" in response to the examiner).
3. Caused by an extensive pontine infarction or profound neuromuscular paralysis, such as Guillain–Barré syndrome.

D. Thalamic lesions.

1. Bilateral lesions interrupting the projections of the intralaminar thalamic nuclei of the ARAS to the frontal lobes can produce an inattentive, unresponsive, but still wakeful state.
2. Paramedian thalamic syndrome.
   a. Lethargic patient with quadriparesis, impaired vertical gaze, and bilateral asterixis.
   b. Caused by bilateral infarction of the dorsal midbrain and thalamus.

E. Nonconvulsive status epilepticus.

1. Occasionally, continual or persistent generalized seizures may occur in the absence of obvious clinical convulsive activity.
2. Subtle clinical manifestations include rhythmical nystagmus, or twitching of an eyelid or part of the face or limb.
3. Obtain an emergent EEG recording and assess the response to IV benzodiazepine boluses.

F. Psychiatric unresponsiveness.

1. Occurs rarely, and remains a diagnosis of exclusion.
2. In the absence of drug overdose, brainstem reflexes and spontaneous breathing should be preserved, and no focal neurological deficits are seen.
3. EEG brain wave frequencies are more similar to that of the awake state than the diffuse EEG slowing typical of toximetabolic coma.
4. Psychiatric patients may become comatose from other medical or neurological disorders as well, or from therapeutic drug therapy (neuroleptic malignant or serotonin syndromes).

IV. MANAGEMENT

A. Initial approach for a comatose patient.

1. Maintain **a**irway, **b**reathing and **c**irculation, since any problems here may be the primary cause of coma, or as secondary complications, may lead to death.
2. Urgently correct any hypothermia, which, if profound, can mimic brain death.
3. If trauma has occurred or is strongly suspected, establish stability of the cervical spine (CT scan) before moving the head, as occurs with testing the oculocephalic (doll's eyes) reflex.
4. Rule out hypoglycemia, especially in diabetic patients, with an immediate fingerstick glucose reading (or empirical infusion of 50% dextrose if immediate testing is not available).
5. Check basic bloodwork (blood count, electrolytes, glucose, renal and liver functions, protime, activated partial thromboplastin time, arterial blood gases, possibly carbon monoxide (CO) level if CO poisoning suspected) and urine drug screen.

B. Comatose patient with suspected hemorrhage.

1. After the initial approach above, perform a brain CT scan without contrast in a known or suspected trauma patient to rule out intracranial hemorrhage.
2. Nontraumatic SAH is suspected with prodromal headache and sudden loss of consciousness.
   a. Rule out SAH with a brain CT scan without contrast.
   b. Perform a lumbar puncture (LP) if SAH is still strongly suspected but not seen on brain CT scan.

c. If SAH is found, request neurosurgical consultation and urgent conventional cerebral angiogram or computed tomography angiogram.

C. Comatose patient with fever or septic syndrome.

1. After the initial approach above, examine the patient for any likely systemic focus (abscess and peritonitis) of infection.
2. Panculture blood and urine, obtain chest X-ray.
3. Perform LP to exclude meningitis (in absence of focal neurological findings, papilledema, bleeding disorder, or local infection over the lumbar spine) and begin initial broad-spectrum antibiotic coverage.
4. If LP is contraindicated, request emergent brain CT scan with and without contrast, and neurosurgery consultation.
5. Especially in the case of *Herpes simplex* encephalitis, a brain MRI scan may help reveal typical frontotemporal lesions.

D. Comatose patient with focal findings on neurological examination.

1. After the initial approach above, exclude hemorrhage with a brain CT scan without contrast.
2. Investigate and treat intracranial hemorrhage or other cause of brain edema or shift.
3. If brain CT scan is normal, obtain brain MRI with and without contrast, including diffusion-weighted sequences, if patient is stable.
4. If brain CT and MRI scans are normal, perform EEG to exclude electrical status epilepticus or postictal state.

E. Comatose patient without focal findings on neurological examination.

1. After the initial approach above, consider administration of IV naloxone or flumazenil, respectively, for possible narcotic or benzodiazepine overdose.
2. If no toximetabolic causes become obvious, obtain a brain CT scan or brain MRI scan if patient is stable.
3. If brain CT and MRI scans are normal, perform an EEG to exclude electrical status epilepticus or postictal state.

Recommended Readings

Castaigne P, Lhermitte F, Buge A, et al. Paramedian thalamic and midbrain infarcts: clinical and neuropathological study. *Ann Neurol*. 1981;10:127–148.

Fisher CM. The neurological examination of the comatose patient. *Acta Neurol Scand*. 1969;45(suppl 36):4–56.

Lee MC, Klassen AC, Resch JA. Respiratory pattern disturbances in ischemic cerebral vascular disease. *Stroke*. 1974;5:612–616.

Merchut MP, Biller J. Assessment of acute loss of consciousness. In: Loftus CM, ed. Neurosurgical Emergencies. 2nd ed. New York, NY: Thieme Medical; 2008:3–10.

Plum F, Posner JB. *The Diagnosis of Stupor and Coma*. 3rd ed. Philadelphia, PA: FA Davis; 1982.

Wallis WE, Donaldson I, Scott RS, et al. Hypoglycemia masquerading as cerebrovascular disease (hypoglycemic hemiplegia). *Ann Neurol*. 1985;18:510–512.

Wijdicks EFM. Altered arousal and coma. In: Wijdicks EFM, ed. *Catastrophic Neurologic Disorders in the Emergency Department*. 2nd ed. Oxford: Oxford University Press; 2004:53–93.

Wijdicks EFM, Bamler WR, Maramattom BV, et al. Validation of a new coma scale: the FOUR score. *Ann Neurol*. 2005;58:585–593.

Young GB, Ropper AH, Bolton CF, eds. *Coma and Impaired Consciousness*. New York, NY: McGraw-Hill; 1998: 307–392.

CHAPTER

6 Approach to the Patient with Seizures

Vicenta Salanova

A. Seizures result from the paroxysmal, hypersynchronous, abnormal activity of neurons in the cerebral cortex. Seizures are common symptoms and can be manifestations of toxic–metabolic abnormalities or of infection, can be secondary to a variety of disorders that affect neuronal function, or can be idiopathic with unknown cause.

1. **Nonrecurrent seizures**—for example, toxic–metabolic, hypoxia.
2. **Recurrent seizures** or epilepsy—inherited, acquired, or structural cortical lesions.

B. The international classification of epileptic seizures consists of two main categories—partial seizures and generalized seizures.

1. **Partial seizures** (focal) result from localized epileptogenic lesions, except in children with benign focal epilepsy, who have no structural lesions. Partial seizures are subdivided as follows:
   a. **Simple partial seizures** if there is preservation of consciousness.
   b. **Complex partial seizures** if there is impairment of consciousness. A partial seizure typically begins as a simple partial seizure consisting of an aura reflecting the site of seizure origin (or ictal spread to the symptomatogenic area) and then evolves into a complex partial seizure. Both simple and complex partial seizures can evolve into secondarily generalized seizures.
2. **Generalized seizures** can be convulsive or nonconvulsive and are subdivided into absence (typical and atypical absences), myoclonic, clonic, tonic, tonic–clonic, and atonic seizures.

C. There is also an **international classification of epilepsy** and epilepsy syndromes. This classification takes into account the age at onset, possible etiologic factors, inheritance, findings at neurologic examination, prognosis, and seizure type (partial or generalized).

1. **Localization-related epilepsy.**
   a. **Idiopathic** (benign childhood rolandic and occipital epilepsy).
   b. **Symptomatic,** which is acquired and based mainly on the anatomic localization.
2. **Generalized epilepsy and syndromes.**
   a. **Idiopathic** with **age-related** onset (e.g., benign neonatal familial convulsions, childhood and juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with grand mal seizures on awakening).
   b. **Symptomatic** (e.g., infantile spasms and Lennox–Gastaut's syndrome). The international classification includes two other categories: (1) epileptic syndromes with both focal and generalized seizures (e.g., acquired epileptic aphasia) and (2) special syndromes (e.g., febrile convulsions). This chapter reviews the etiology, clinical manifestations, evaluation, and differential diagnoses of some of these types of seizures with emphasis on patients with partial seizures.

I. ETIOLOGY

A. Toxic–metabolic.

1. **Systemic illness.** Hypoglycemia, nonketotic hyperglycemia, hypoxia, hypocalcemia (in patients with or without a history of hypoparathyroidism), hyponatremia (inappropriate antidiuretic hormone syndrome and water intoxication), hypomagnesemia, uremia and hepatic failure, sickle-cell anemia, thrombotic thrombocytopenic purpura, Whipple's disease.

2. **Drugs and toxins.** Cocaine, amphetamines, phencyclidine, lidocaine, lead poisoning. Others can lower the seizure threshold and increase the risk of seizures usually among patients with other predisposing factors (tricyclics, theophylline, phenothiazine, and penicillins).
3. **Withdrawal syndromes.** Alcohol, hypnotics.
4. **Pyridoxine deficiency.**

B. **Acquired structural lesions.**

1. **Infection.** Brain abscess, meningitis, encephalitis (e.g., herpes simplex encephalitis), postinfectious encephalomyelitis, cysticercosis, opportunistic infections in AIDS, neurosyphilis.
2. **Vascular.** Vasculitis (systemic lupus erythematosus, hypersensitivity, and infectious vasculitis), ischemic or hemorrhagic cerebrovascular disease, cerebral venous thrombosis, arteriovenous malformation, cavernous angioma.
3. **Trauma.** Usually penetrating, subdural hematoma.
4. **Neoplasms** and other lesions. Primary or metastatic tumors, hamartomas, cortical dysplasia.
5. **Mesial temporal sclerosis.** Usually postfebrile convulsions.
6. **Other.** Alzheimer's disease, Creutzfeldt–Jakob's disease, and in rare instances, multiple sclerosis.

C. **Familial.**

1. Primary generalized epilepsy.
2. Benign focal epilepsy of childhood.
3. Febrile convulsions.
4. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).
5. Familial temporal lobe epilepsy (FTLE).

D. **Other genetic syndromes** associated with seizures (tuberous sclerosis and neurofibromatosis), disorders of amino acid, lipid, and protein metabolism (e.g., phenylketonuria, maple syrup urine disease, and porphyria).

II. CLINICAL MANIFESTATIONS

A. **Metabolic–toxic and hypoxic insults.** Patients with seizures attributable to metabolic or toxic causes have generalized tonic–clonic seizures, but focal seizures and epilepsia partialis continua can occur with nonketotic hyperglycemia. Posthypoxic coma usually causes multifocal myoclonus; however, periodic lateralized epileptiform discharges (PLEDs) may be seen, at times associated with focal motor seizures.

B. **Meningitis and encephalitis** can cause either generalized or focal seizures with secondarily generalized seizures. Patients with herpes simplex encephalitis often have complex partial seizures typical of those of temporal lobe origin. The EEG shows focal slowing in one or both temporal regions and PLEDs. MRI shows hypodense lesions in one or both temporal lobes.

C. **Partial seizures** (functional–anatomic classification of epilepsy). Clinical features and EEG findings indicate focal origin.

1. **Temporal lobe seizures** are the most common partial seizures. In 30% of these patients, the seizures are refractory to medical treatment.
   a. **Signs and symptoms.** The findings at neurologic examination often are normal, except for memory dysfunction, which can be seen in patients with bitemporal epilepsy. Most of these patients have an epigastric aura (nausea, an epigastric rising sensation, stomach upset, or even pain). Other aurae consist of fear, complex visual or auditory hallucinations, déjà vu, and olfactory and gustatory sensations. The clinical manifestations are stereotypical, and most patients have one seizure type. Most patients exhibit staring, unresponsiveness, and oroalimentary and gestural automatism. Some patients also have contralateral arm dystonic posturing. Ictal or postictal language difficulties also have lateralizing value. Ictal speech occurs in patients with seizures arising from the nondominant temporal lobe. Patients with seizures originating from the dominant temporal lobe may exhibit ictal and postictal dysphasia.

b. **Etiologic factors and pathologic features.** Mesial temporal sclerosis is the most common pathologic finding. There is a strong association between mesial temporal sclerosis and prolonged complex febrile seizures in patients younger than 5 years of age. There usually is a silent interval between the occurrence of febrile seizures and the onset of mesial temporal lobe epilepsy, which often begins toward the end of the first decade of life or soon after. Other pathologic findings include tumors such as ganglioglioma, cortical dysplasia, and cavernous malformation. As many as 15% of patients with medically refractory temporal lobe epilepsy have evidence of a dual pathologic process. Mesial temporal sclerosis can occur with temporal lobe developmental lesions such as cortical dysplasia and subependymal heterotopia.

c. **EEG findings** include epileptiform discharges over the anterior temporal region and often polymorphic slowing. About 30% to 40% of these patients have bitemporal independent interictal epileptiform discharges, usually with predominance on the side of ictal onset.

d. **Imaging studies**. MRI volumetric studies usually show a smaller hippocampus and increased signal intensity on T2-weighted images that are indicative of hippocampal sclerosis. These changes can be seen in as many as 80% of patients with refractory temporal lobe epilepsy.

e. **Secondarily generalized** tonic–clonic seizures and convulsive status epilepticus can occur; nonconvulsive complex partial status epilepticus is rare.

f. Patients with temporal lobe seizures should be differentiated from patients with **FTLE**. The first series described FTLE as a benign disorder with late age of onset, excellent outcome, and normal finding on the MRI of the head. A second report, however, showed that some cases of FTLE were refractory to medical treatment, requiring surgical treatment. The most recent report concluded that FTLE is a clinically heterogeneous syndrome. The authors found hippocampal atrophy in 57% of their patients, including those with a benign course or remission of seizures. They concluded that the findings indicated the presence of a strong genetic component in the development of mesial temporal sclerosis in the families studied.

2. **Focal motor seizures**. These seizures originate in the vicinity of the rolandic motor cortex. Consciousness is preserved.

a. **Signs and symptoms**. Examination may show contralateral mild hemiparesis or hyperreflexia. Seizures commonly begin with focal contralateral twitching of the face or hand and then spread to involve the rest of the extremity. When seizures originate in the nondominant hemisphere, patients usually are able to speak during the seizures. When seizures originate in the dominant hemisphere, patients may have ictal and postictal aphasia. Clonic eye movements, blinking, and conscious contraversion also may occur. Ictal focal motor manifestations, postictal hemiparesis, and postictal aphasia are contralateral to the side of seizure onset. Some patients have continuous focal motor activity (epilepsia partialis continua lasting weeks, months, or even years).

b. **Imaging studies**. Focal structural lesions are common.

c. **EEG** shows focal slowing and focal epileptiform discharges over the frontal lobe; however, some patients have no epileptiform discharges on scalp recordings or have bifrontal epileptiform abnormalities.

d. Patients with focal motor seizures have to be differentiated from patients with benign rolandic epilepsy with centrotemporal spikes, which begins between the ages of 3 and 13 years. These children have normal findings at neurologic examination and imaging studies. They have nocturnal generalized seizures and partial seizures beginning in the face with preservation of consciousness, at times with speech arrest. The EEG shows centrotemporal, high-amplitude, broad, sharp waves and slow discharges, with a horizontal dipole, occurring predominantly during sleep. The prognosis is excellent.

3. **Supplementary motor seizures** originate in the supplementary motor cortex, which is located in the mesial frontal lobe anterior to the primary motor leg area.

a. **Signs and symptoms**. Findings at examination usually are normal. Almost one-half of these patients have a somatosensory aura consisting of tingling or numbness of

the extremities, which can be contralateral or bilateral. These patients have unilateral or bilateral tonic posturing of the extremities at onset, vocalization, speech arrest, and laughter. Other manifestations include fencing posture, thrashing, kicking, and pelvic movements. Responsiveness is preserved unless the seizure evolves into a secondarily generalized tonic–clonic seizure. Supplementary motor seizures are common during sleep and are of short duration without postictal confusion or amnesia.

b. **Imaging studies**. MRI of the head may show lesions in the supplementary motor area.

c. The **EEG** may show epileptiform discharges over the vertex, but some patients may have no interictal epileptiform discharges on scalp recordings. Ictal recordings often are nonlateralized. A few patients may have no ictal EEG changes during scalp recordings.

4. **Complex partial seizures of frontal lobe origin.**

a. **Signs and symptoms**. The examination usually is normal. Patients may have a cephalic aura that is followed by staring or looking ahead, unconscious contraversion, and complex motor automatism such as bicycling, kicking, thrashing, running, and bouncing up and down. Vocalization and tonic posturing may occur toward the end of the seizure as manifestations of ictal spread to the supplementary motor area. Complex partial (nonconvulsive) status epilepticus, manifested by alteration of consciousness with automatic behavior often in a cyclical manner lasting hours to days, also may occur. Secondarily generalized tonic–clonic seizures and convulsive status epilepticus are believed to be more common in patients with frontal lobe seizures.

b. **Imaging studies**. MRI may show lesions in the frontopolar, dorsolateral, orbitofrontal, and other frontal regions.

c. The **EEG** may show focal slowing and interictal epileptiform discharges over one frontal lobe, lateralized to one hemisphere, or bilateral frontal epileptiform abnormalities.

d. These patients with acquired frontal lobe epilepsy should be differentiated from those with **ADNFLE**. In ADNFLE, the seizures begin in childhood and usually persist through adult life. They occur in clusters during sleep and are characterized by vocalization, thrashing, hyperkinetic activity, or tonic stiffening. Patients have a normal findings at neurologic examination and on imaging studies. An ictal EEG may show bifrontal epileptiform discharges. The seizures usually respond to carbamazepine monotherapy. These seizures often are misdiagnosed as parasomnia or familial dyskinesia.

5. **Occipital lobe seizures** are rare, but they may be difficult to differentiate from seizures originating from the posterior temporal lobe. These patients have to be differentiated from patients with benign occipital epilepsy, the onset of which is in childhood and has similar symptoms but no occipital lesions. The age at onset of benign occipital epilepsy ranges from 15 months to 17 years (with a peak between 5 and 7 years), and more than one-third of patients have family histories of epilepsy.

a. **Signs and symptoms.** Occipital manifestations are common. Patients may have visual field defects, visual aurae consisting of elementary visual hallucinations described as colored flashing lights, or ictal blindness. Other manifestations include contralateral eye deviation, a sensation of eye movement, nystagmoid eye movements, and blinking. After the occipital manifestations, many patients have typical temporal lobe automatism as well as focal motor seizure activity resulting from ictal spread to the temporal and frontal lobes. Because of these different spread patterns, many patients have more than one type of seizure. Almost two-thirds of patients have lateralizing clinical features, such as contralateral head deviation and visual field defects contralateral to the epileptogenic zone.

b. **Imaging studies**. On CT scans and MRIs, many patients have occipital lesions ipsilateral to the epileptogenic zone.

c. The **EEG** may show focal slowing and epileptiform discharges over one occipital lobe. However, most often the EEG shows posterior temporal epileptiform discharges. Some patients have bilateral posterior temporal–occipital epileptiform abnormalities.

6. **Parietal lobe seizures** are uncommon.
   a. **Signs and symptoms**. The examination may show contralateral impaired two-point discrimination, but more often the findings are normal. These patients have somatosensory aurae described as contralateral tingling or numbness and painful and thermal sensations. Other aurae consist of disturbances of body image, a sensation of movement in one extremity, or a feeling that one extremity is absent. Vertiginous sensations and visual illusions can occur, as can an aphasic aura. Some of these patients have seizures of multiple types as a result of ictal spread to the temporal and frontal lobes. Tonic posturing of extremities, focal motor clonic activity, head and eye deviations, and temporal lobe automatism are commonly observed.
   b. **Imaging studies**. MRI may show focal lesions in the parietal lobe.
   c. The **EEG** most often shows lateralized epileptiform discharges to one hemisphere rather than localized discharges.

D. **Primary (idiopathic) generalized epilepsy.** There is usually a family history of epilepsy. The first clinical manifestations indicate involvement of both cerebral hemispheres. This form of epilepsy can be **convulsive** or **nonconvulsive.**

1. **Childhood absence epilepsy** begins between the ages of 4 and 8 years. The findings at neurologic examination are normal.
   a. **Signs and symptoms**. There is a brief loss of consciousness, usually lasting 10 seconds or less and almost always lasting less than 30 seconds. There is no aura or postictal confusion. Blinking, brief facial twitching, or other clonic component, decreased postural tone, and automatism such as swallowing, lip smacking, and fumbling with clothes are common. About 40% to 50% of patients also may have tonic–clonic seizures.
   b. **The EEG** shows the typical generalized, bilaterally synchronous 3-Hz spike–wave epileptiform discharges. Hyperventilation for 3 to 5 minutes often provokes an absence seizure with typical generalized, bifrontally dominant, regular, synchronous 3-Hz spike–wave complexes with abrupt onset and termination. In some patients, the epileptiform discharges may be maximum over the posterior head regions.
   c. **The prognosis** is favorable, and for many patients the seizures remit in adolescence. The prognosis is less favorable if tonic–clonic seizures occur.
   d. **Absence status.** Rare patients may have prolonged confusion that lasts hours or all day and is associated with continuous 3-Hz spike–wave discharges.
2. **Juvenile absence epilepsy** is less common than childhood absence epilepsy.
   a. The **clinical manifestations** are similar, but seizures begin during puberty or later. The absences tend to occur on awakening and are not as frequent as those in the childhood form. Myoclonic seizures also may occur.
   b. The **EEG** may show generalized 3-Hz spike–wave discharges or higher-frequency (4 to 5 Hz) discharges.
   c. The **prognosis** is not as favorable as in the childhood form, and generalized tonic–clonic seizures are more frequent. Absence status is also more frequent than in the childhood form.
3. **Juvenile myoclonic epilepsy.** Age at onset is in the second decade. The findings at neurologic examination are normal. The diagnosis often is missed because of failure to recognize the myoclonic jerks.
   a. **Signs and symptoms.** These patients have awakening myoclonic and generalized tonic–clonic seizures. Absence seizures occur in 15% of patients. During brief myoclonic jerks, consciousness is preserved. Myoclonic seizures may precede the onset of generalized tonic–clonic seizures by a few years, or they may have simultaneous onset. The generalized tonic–clonic seizures usually follow a series of myoclonic seizures. Seizures may be precipitated by sleep deprivation or alcohol intake.
   b. The **EEG** shows generalized polyspike and wave discharges in most patients. Some patients are photosensitive and have photoparoxysmal responses. During the myoclonic jerks, the EEG shows abrupt onset of high-amplitude polyspike and wave complexes lasting from 2 to 10 seconds.
   c. **Prognosis**. Although these patients have an excellent response to valproic acid, the electroclinical trait persists for life, and most patients need lifelong treatment.

4. **Generalized tonic–clonic seizures**. A patient with primary generalized tonic–clonic seizures usually has a family history of epilepsy. The findings at neurologic examination are normal. Age at onset usually is during puberty.
   a. **Signs and symptoms**. There is no aura. A few patients may have a prodrome (nervousness and irritability) hours before the seizure. The seizure begins with brief tonic flexion of the axial muscles and muscular contraction of the extremities followed by a longer period of tonic extension of the axial muscles. The mouth is closed, and this may lead to tongue biting. Apnea can occur as a result of contraction of the respiratory muscles. The arms are semiflexed, and the legs are extended. After the tonic phase, there is diffuse tremor, and then there is a clonic phase. Autonomic changes usually occur at the end of the tonic phase. Heart rate and blood pressure can more than double during the tonic phase. There is also increased bladder pressure.
   b. **Complications** during a prolonged tonic–clonic seizure may include tongue biting, dislocation of shoulders, vertebral compression fractures, aspiration pneumonia, and even sudden death. The mechanism of sudden death is unclear; several factors, such as apnea, pulmonary edema, and cardiac arrhythmias, may be involved.
   c. The **EEG** shows generalized 4- to 5-Hz spike–wave activity, or multiple spike–wave complexes. More irregular spike–wave discharges can occur. The likelihood of recording the epileptiform discharges increases if the EEG is obtained 1 to 5 days after a seizure. Some patients have a photoparoxysmal response with bisynchronous, generalized irregular spike and spike–wave discharges. EEG ictal changes show generalized low-voltage fast activity (recruiting rhythm) followed by high-amplitude generalized polyspike or polyspike and wave discharges. During the clonic phase, high-amplitude polyspike or polyspike and wave discharges alternate with low-amplitude slowing. Postictally, there is low-amplitude slowing.
   d. **Generalized tonic–clonic status epilepticus** begins with recurrent, brief tonic–clonic seizures without full recovery of consciousness or with a prolonged generalized tonic–clonic seizure lasting 30 minutes.

E. Secondary (symptomatic) generalized epilepsy. These patients have multifocal cortical abnormalities, including infantile spasms (West's syndrome) and Lennox–Gastaut's syndrome.

1. **West's syndrome.** The onset usually is between 3 and 6 months of age and always before 1 year. Some infants have no identifiable etiologic factors (cryptogenic subgroup). Symptomatic West's syndrome is more common and can result from trauma, infection, Down's syndrome, tuberous sclerosis, phenylketonuria, and other disorders. These infants have frequent infantile spasms, developmental delay, and a characteristic EEG pattern (hypsarrhythmia).
2. **Lennox–Gastaut's syndrome** is one of the most severe epileptic syndromes. These children usually have developmental delay, neurologic deficits, and seizures of multiple types, which are often medically refractory (drop attacks, atypical absence, myoclonic, tonic, and tonic–clonic seizures). The EEG shows generalized slow (<2.5 Hz) spike–wave discharges.
   a. **Drop attacks** represent atonic seizures and are characterized by sudden loss of tone, at times preceded by a generalized clonic jerk. There is head drop, and often the child collapses. The ictal EEG shows an electrodecremental response.
   b. **Atypical absences** usually last longer than typical absences and are commonly associated with motor findings and postictal confusion. They are more common during drowsiness and are not usually activated by hyperventilation. The EEG shows generalized slow spike–wave discharges and diffuse slowing of the background.
   c. **Absence status** is common. Patients come to medical attention with prolonged absences (spike–wave stupor), blinking, and at times facial twitching with continuous generalized spike–wave discharges.
   d. **Tonic seizures** are common in Lennox–Gastaut's syndrome. The arms are elevated in a semiflexed position, and there is impairment of consciousness and autonomic changes.

III. EVALUATION

A. History.

1. The following should be documented: **age at onset** and **frequency** of seizures, **family history** of epilepsy, psychosocial history, possible etiologic factors such as history of head trauma, difficult birth, febrile seizures, meningitis, or encephalitis. **Precipitating factors** include medical illnesses that can lead to metabolic abnormalities and exposure to drugs or toxins.
2. The **presence and type of aura,** detailed description of the seizure by a family member, presence of automatism, ictal speech, dystonic or tonic posturing, postictal language difficulties, Todd's paralysis, or the presence of myoclonus can help to **differentiate focal from generalized seizures.**
3. **Response to anticonvulsants** and possible side effects.

B. Physical examination.

1. **Detailed examination,** including the skin, for signs of neurocutaneous lesions associated with seizures, such as neurofibromatosis, tuberous sclerosis, and Sturge–Weber's syndrome. Cranial bruits may be present in patients with arteriovenous malformations, and cervical bruits in patients with seizures resulting from cerebrovascular disease.
2. **Limb asymmetry** suggestive of injuries early in life. **Focal neurologic deficits,** such as subtle hemiparesis, hyperreflexia, decreased two-point discrimination, or visual field defects, may suggest the location of the epileptogenic lesion. **Memory deficits** can be elicited in some patients with bitemporal epilepsy.

C. Laboratory studies include complete blood cell count; a Venereal Disease Research Laboratory test; measurement of erythrocyte sedimentation rate and blood levels of glucose, calcium, sodium, and magnesium; liver and renal function tests; drug and toxicology screening if indicated by the history or examination findings; and HIV testing for patients with risk factors.

D. CSF examination is performed if vasculitis or infection is suspected or if the serologic result is positive for syphilis.

E. The **EEG** is essential to confirm the diagnosis of epilepsy and to characterize the seizure type. It usually shows focal slowing and epileptiform abnormalities in patients with partial seizures or generalized epileptiform discharges in those with generalized seizures. Seizures are rarely recorded on routine EEGs. The exception is absence seizures, which can be precipitated by hyperventilation. Metabolic encephalopathy associated with seizures usually have diffuse slowing or periodic patterns, such as triphasic waves, in patients with hepatic or renal failure.

1. **Activation procedures,** such as photic stimulation, hyperventilation, and sleep, are performed.
2. **Special electrodes**. Earlobe, anterior temporal, or zygomatic electrodes often are used. Nasopharyngeal electrodes are traumatic and produce artifacts, and they should not be used. Sphenoidal electrodes are reserved for patients undergoing presurgical evaluation.
3. **Video EEG recordings**. In some patients with recurrent seizures and no interictal epileptiform discharges on serial EEGs, prolonged video EEG recording may be needed to confirm the diagnosis and to characterize the seizure type.

F. Imaging studies. When the history, neurologic examination, EEG findings, and seizure type suggest partial seizures, the procedure of choice is **MRI of the head.** Although the CT of the head may be helpful, some patients with partial seizures have lesions that do not appear on CT scans, such as hamartoma, cortical dysplasia, low-grade glioma, or cavernous malformation.

IV. DIFFERENTIAL DIAGNOSIS

The **differential diagnosis** includes many neurologic, psychiatric, and medical disorders. The most common are psychogenic seizures and syncopal episodes.

A. **Syncope** is defined as a brief episode of loss of consciousness and postural tone as a result of a transient decrease in cerebral blood flow (see Chapter 7). Episodes last a few seconds. Brief tonic–clonic movements and incontinence of urine and feces can occur (convulsive syncope). An EEG during the prodromal period (light-headedness) shows diffuse high-amplitude slowing, and when tonic or clonic activity occurs, the EEG result is isoelectric.
B. **Psychogenic seizures** are suspected when a patient has seizures precipitated by stress when others are present, no response to anticonvulsants, seizures of long duration up to 15 or 30 minutes or even hours, side-to-side head movements, pelvic thrusting, arrhythmic jerking, bilateral motor activity with preservation of consciousness, bizarre and aggressive behavior, and crying. There is no postictal confusion after generalized tonic–clonic jerking. However, some of these symptoms (bizarre complex automatism, pelvic thrusting, bilateral motor activity) can occur among patients with complex partial seizures of frontal lobe origin and supplementary motor seizures.
C. **Panic attacks.**
D. **Cerebrovascular disorder.** Transient global amnesia.
E. **Basilar migraine.**
F. **Sleep disorder.** Narcolepsy.
G. **Movement disorder.** Myoclonus, choreoathetosis, familial paroxysmal dystonia.
H. **Paroxysmal vertigo.**
I. **Toxic–metabolic disorder.** Alcohol withdrawal, hypoglycemia.
J. **Daydreaming episodes.**

V. DIAGNOSTIC APPROACH

A. The **history and examination** are central to determine the type of seizure (generalized or focal, psychogenic, related to syncope or metabolic causes, and so on), obtain descriptions of the aura (if present) and the seizure by a witness, and identify subtle neurologic deficits. It is helpful to ask a family member to mimic the seizure. After the initial evaluation, a presumptive etiologic diagnosis and a tentative seizure classification often are possible and should determine the extent of the evaluation.
B. **Laboratory evaluation** should include serum electrolytes, baseline renal and hepatic function tests to rule out metabolic causes, drug screening, and other tests as indicated by the history and examination findings.
C. If syncope is suspected, **ECG** and **Holter's monitoring** are performed as indicated by the history and examination findings. More extensive evaluation for cardiac causes of syncope may be needed.
D. **Sleep and awake EEGs** are obtained with activation procedures (hyperventilation and photic stimulation) and special electrodes. An ambulatory EEG may be helpful in the evaluation of patients with suspected seizures or pseudoseizures or suspected convulsive episodes of syncope.
E. **Prolonged video EEG** may be needed to confirm the diagnosis, characterize the seizure type, and exclude psychogenic seizures. Complex partial seizures of frontal lobe origin and supplementary motor seizures often are misdiagnosed as psychogenic seizures, and ictal recordings often are needed.
F. **Sleep studies** (multiple sleep latency test and polysomnography) may be needed in the evaluation of some patients with suspected sleep disorders.
G. **MRI** should be performed on patients with partial seizures and secondary (symptomatic) generalized epilepsy.

VI. REFERRAL

A. For patients with recurrent seizures, an initial **neurologic consultation,** including an EEG to clarify the seizure type, allows the proper choice of anticonvulsants.

B. When the diagnosis remains unclear after the initial evaluation or there is lack of response to anticonvulsants, the patient should be referred to a **comprehensive epilepsy center.** Evaluation at such centers includes prolonged video EEG with sphenoidal electrodes. It is important to emphasize that patients with poorly controlled epilepsy have a higher mortality rate than does the general population. Death usually is caused by accidents, status epilepticus, sudden unexplained death, cardiac arrhythmias, and suicide. However, when seizures are completely controlled after surgery, the mortality rate is not different from that of the age-matched general population.

1. Because the treatment and prognosis are based on the seizure type and epileptic syndrome, **ictal recordings** are invaluable and allow the proper choice of anticonvulsants.

2. Ictal recordings are the most effective way to diagnose psychogenic seizures, but patients with psychogenic seizures may also have epileptic seizures, and **all the habitual seizure types** should be recorded. To compound the problem, some patients with supplementary motor seizures and other simple partial seizures may have no ictal EEG changes on scalp recordings, or the EEG activity may be obscured by muscle artifacts. Inpatient prolonged video EEG recordings with reduction of anticonvulsants may clarify the diagnosis by recording secondarily generalized seizures.

C. Identification of surgical candidates. Approximately 30% of cases of complex partial seizures of temporal lobe origin are refractory to medical treatment, and many patients benefit from surgery. Prolonged video EEG, MRI with volumetric studies, and tests of focal functional deficits (FDG-PET scans) are conducted at epilepsy centers to identify surgical candidates.

D. Patients with medically refractory temporal lobe epilepsy are the largest group of patients undergoing epilepsy surgery, and 70% to 80% of these patients become seizure free after surgery. A longitudinal study of a large number of patients who underwent temporal resection showed the lasting benefits of epilepsy surgery. The best surgical outcome was observed among patients with small lesions such as cavernous malformation, followed by patients with mesial temporal sclerosis. Studies also have shown considerable improvement in the quality of life of patients who became seizure free after surgery.

E. Neurostimulators in epilepsy. Vagal nerve stimulation was approved for the treatment of patients with refractory partial epilepsy who are not candidates for surgical resection. In clinical trials, 30% to 40% of patients with medically refractory partial seizures had a reduction in seizures of at least 50%.

The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsytrial (SANTE trial) reported the results of 110 patients who participated in a multicenter, double blind, randomized controlled trial of bilateral stimulation of the anterior nuclei of the thalamus for localization-related epilepsy, and found benefit that persisted through 2 years. Complex partial and "most severe seizures" were significantly reduced by stimulation. Long-term follow-up showed continuous improvement; the median percent reduction from base line at 1 year was 41%, at 2 years was 56%. Over the entire study, 14% of patients were seizure free for at least 6 months. There were no unanticipated adverse device effects. The Liverpool seizure severity scale and quality of life measure also showed statistically significant improvement over baseline by 1 year, which continued to be significant at 2 and 3 years ($P<0.001$). Neuropsychological profiles remained stable. Deep brain stimulation (DBS) of the thalamus is helpful for people with medically refractory partial and secondarily generalized seizures. Based on the results of the SANTE trial, DBS for epilepsy was recently approved in Europe, but remains investigational in the USA.

Recommended Readings

Berkovic S, McIntosh A., Howell RA, et al. Familial temporal lobe epilepsy: a common disorder identified in twins. *Ann Neurol.* 1996;40:227–235.

Cendes F, Cook MJ, Watson C, et al. Frequency and characteristics of dual pathology in patients with lesional epilepsy. *Neurology.* 1995;45:2058–2064.

Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of the thalamus for treatment of refractory epilepsy. *Epilepsia.* 2010;51(5):899–908.

French JA, Williamson PD, Thadani VM, et al. Characteristics of medial temporal lobe epilepsy, I: results of history and physical examination. *Ann Neurol.* 1993;34:774–780.

Gloor P, Olivier A, Quesney LF, et al. The role of the limbic system in experiential phenomena of temporal lobe epilepsy. *Ann Neurol.* 1982;12:129–144.

Lüders H, Lesser R, eds. *Epilepsy: Electroclinical Syndromes.* London, UK: Springer-Verlag; 1987.

Morris H III, Dinner DS, Lüders H, et al. Supplementary motor seizures: clinical and electrographic findings. *Neurology.* 1988;38:1075–1092.

Penfield W, Jasper H. *Epilepsy and the Functional Anatomy of the Human Brain*. Boston, MA: Little Brown; 1954.

Salanova V, Andermann F, Olivier A, et al. Occipital lobe epilepsy: electroclinical manifestations, electrocorticography, cortical stimulation and outcome in 42 patients treated between 1930 and 1991. *Brain.* 1992;115:1655–1680.

Salanova V, Andermann F, Rasmussen T, et al. Parietal lobe epilepsy: clinical manifestations and outcome in 82 patients treated surgically between 1929 and 1988. *Brain*. 1995;118:607–627.

Salanova V, Markand O, Worth R. Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. *Epilepsia.* 2002;43(2):170–174.

Salanova V, Morris HH, Van Ness P, et al. Frontal lobe seizures: electroclinical syndromes. *Epilepsia.* 1995;36:16–24.

Salanova V, Worth R. Neurostimulators in epilepsy. *Curr Neurol Neurosci Rep.* 2007;7:315–319.

Scheffer I, Bhatia K, Lopez-Cendes I, et al. Autosomal dominant frontal lobe epilepsy: a distinctive clinical disorder. *Brain.* 1995;118:61–73.

Wyllie E. ed. *The Treatment of Epilepsy: Principles and Practice*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

CHAPTER

7 Approach to the Patient with Syncope

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Syncope is usually defined as transient loss of consciousness and postural tone followed by spontaneous recovery. It has been proposed that application of this term be limited to the subgroup of these related to transient global cerebral hypoperfusion (distinguishing transient loss of consciousness from other causes such as seizure, trauma, or psychogenic causes); however, usage of the term varies. In the United States alone, up to 5% of all emergency room visits and hospital admissions are due to syncope, thereby accounting for approximately 300,000 emergency department visits and 100,000 admissions per year. More than a million individuals a year are evaluated for syncope and related injuries (e.g., falls, fractures, etc.), thus imposing a high cost burden on the health care system.

I. ETIOLOGY

Syncope broadly defined is most commonly cardiovascular in etiology. Most often, a generalized or local cerebral impairment of blood/oxygen delivery causes the loss of consciousness. Despite frequent referral for neurologic investigation after syncope, primary neurologic causes of syncope are uncommon (excepting neurocardiogenic/vasovagal episodes).

Even in cases where seizure-like motor activity is witnessed after the loss of consciousness, these may be a consequence of a cardiovascular etiology and an assessment for such is often warranted. Other causes of transient loss of consciousness may present similarly and at times may be difficult to distinguish on initial evaluation.

Cardiovascular causes include decreased cardiac output secondary to abnormalities in heart rate and/or stroke volume, impairment of cerebral blood flow, and decreased blood pressure related to hypovolemia or decreased peripheral vascular resistance. Any medical condition causing one of these features may lead to the development of syncope. As shown in Table 7.1, the causes of syncope can be classified into broad categories: **neurally mediated syncope, orthostatic hypotension, cardiac arrhythmias, structural heart disease,** and **cerebrovascular steal syndromes.** Based on pooled data from five studies, the incidence of the major causes of syncope is shown in Table 7.2.

Often multiple mechanisms can contribute to the syncope. For example, medications or postprandial fluid shifts can exacerbate mild preexisting orthostatic hypotension, sinus node dysfunction, and impaired autoregulation of cerebral blood flow. This is especially true in the elderly in whom syncope is commonly multifactorial.

A. Neurally mediated syncope, also referred to as neurocardiogenic or vasodepressor syncope, is common, and results from the activation of a reflex that produces a significant vasodilatory (vasodepressor) and/or bradycardic (cardioinhibitory) response. Typically, it occurs after prolonged standing or sitting and may be reproduced on tilt-table testing. Long-term follow-up studies have shown that neurally mediated syncope carries a benign prognosis and a similar survival outcome to those patients with no history of syncope. Several different etiologies can lead to neurally mediated syncope as shown in Table 7.1. Almost all of these etiologies can be diagnosed by a carefully taken history. Classic vasovagal syncope may be considered in this group, and usually occurs in the setting of emotional or orthostatic stress, although it can also have an atypical presentation with no clear triggering events or premonitory signs. A careful history should also diagnose the etiology of several causes of situational syncope (e.g., postprandial, postmicturition, postdefecation, etc.). Syncope due to carotid sinus hypersensitivity occurs in the setting of inadvertent mechanical pressure on the carotid sinus and can

TABLE 7.1 Causes of Syncope

Neurally Mediated
Vasovagal syncope
Carotid sinus syncope
Situational syncope (cough, swallow, micturition, defecation, postprandial, etc.)
Glossopharyngeal neuralgia

Orthostatic Hypotension
Volume depletion
Medications
Autonomic failure syndromes
  Primary autonomic failure (Parkinson's disease, MSA)
  Secondary autonomic failure (diabetes mellitus, amyloidosis)
Alcohol or illicit drugs
Post-exercise

Cardiac Arrhythmias
Sinus node dysfunction
AV conduction system disease
Paroxysmal supraventricular and ventricular tachycardias
Channelopathies (long QT syndrome, Brugada's syndrome)
Arrhythmogenic right ventricular dysplasia
Drug-induced (torsades de pointes, bradycardia)
Implantable device malfunction (pacemaker or defibrillator)

Structural Cardiovascular Disease
Obstructive valvular disease, particularly aortic stenosis
Hypertrophic obstructive cardiomyopathy
Atrial myxoma
Aortic dissection
Pericardial tamponade
Pulmonary embolism

Cerebrovascular
Subclavian steal syndrome
Stroke/TIA (uncommon)

Metabolic and other conditions:
Electrolyte derangements
Hypoglycemia
Hypoxemia
Anemia

TABLE 7.2 Incidence of Major Causes of Syncope

Cause	Percentage
Vasovagal	18
Situational	5
Orthostatic	8
Cardiac	18
Medication	3
Psychiatric	2
Neurologic	10
Carotid sinus	1
Unknown	34

be reproduced by carotid sinus massage. Glossopharyngeal neuralgia may present with syncope associated with painful swallowing.

B. Orthostatic hypotension can cause inadequate cerebral perfusion leading to syncope upon rising from a sitting or supine to an upright position. The most common mechanism of hypotension is the loss of peripheral vascular tone due to the failure of the autonomic nervous system to maintain peripheral vascular resistance. This can occur due to a primary dysfunction of the autonomic nervous system associated with several neurodegenerative conditions (multiple systems atrophy [MSA]) or due to diseases causing secondary autonomic nervous system failure (e.g., diabetes, amyloidosis, etc.). MSA encompasses a group of sporadic progressive neurologic disorders characterized clinically by autonomic dysfunction (i.e., orthostatic hypotension, impotence, urinary retention or incontinence, etc.), parkinsonism, and ataxia in any combination. Medications, alcohol, and drug toxicity should also be considered when evaluating orthostatic hypotension. Volume depletion (e.g., dehydration, hemorrhage, Addison's disease, etc.) may cause orthostatic syncope.

C. Cardiac arrhythmias often present with syncope due to a decrease in cardiac output. This can occur in bradycardia (e.g., sinus arrest, heart block, etc.) or tachycardia (e.g., nonsustained ventricular tachycardia/fibrillation). It is relatively uncommon for supraventricular tachycardias to cause syncope in the absence of other structural heart disease or the Wolff–Parkinson–White's syndrome (i.e., preexcited atrial fibrillation). Arrhythmic syncope may indicate a risk for sudden death and should be aggressively managed. In patients with congestive heart failure (CHF), syncope is associated with an increased risk for cardiovascular and total mortality.

D. Structural heart disease can cause syncope due to the inability to produce sufficient cardiac output to match demand. Obstructive valvular heart disease and hypertrophic cardiomyopathy are common etiologies. Primary pump failure due to myocardial dysfunction can also lead to syncope; however, associated ventricular arrhythmias are a more common cause. Other less common conditions include atrial myxoma, pericardial tamponade, and acute aortic dissection.

E. Cerebrovascular causes of syncope are rare. These include steal syndromes, such as subclavian steal, in which cerebral blood is shunted away from the brain. Obstruction of cerebral blood flow is a rare cause of true syncope. Most carotid artery distribution transient ischemic attacks (TIAs) cause unilateral visual impairment, weakness, or loss of sensation. Posterior circulation TIAs generally manifest as diplopia, vertigo, ataxia, or "drop attacks," but not loss of consciousness. Rare patients with TIA may have transient loss of consciousness, but isolated syncopal episodes without accompanying neurologic symptoms should generally not be ascribed to a TIA.

F. Psychogenic syncope occurs without any substantial changes in hemodynamics and is often associated with a prior significant psychologic event. Physical causes must be excluded. It and other causes are included in the differential diagnosis of transient loss of consciousness, but are usually distinguished from true syncope.

G. Syncope of unknown origin is a legitimate diagnosis made after a careful history, physical examination, and selected laboratory tests have failed to elucidate a specific etiologic factor. This diagnosis is clinically useful because it is associated with a prognosis that is considerably better than that of patients who have identifiable cardiac or neurologic causes of syncope. Although long-term follow-up studies have shown that patients with syncope and a history of cardiac or neurologic disease have increased long-term mortality, those patients with syncope of unknown causation have a distinctly better prognosis.

II. EVALUATION

Initial evaluation of syncope should address three key questions:

- **Is the loss of consciousness attributable to true syncope or to other nonsyncopal factors?** A careful history is crucial for making the diagnosis and excluding nonsyncopal etiologies. Table 7.3 lists some conditions that are commonly distinguished from syncope, some of which are associated with a transient loss of consciousness.
- **Are there any distinguishing features in the history that may suggest the diagnosis?** Table 7.4 lists features of vasovagal syncope, seizures, and cardiac syncope.
- **Does the patient have heart disease?** Patients with syncope have a fairly benign clinical course in the absence of heart disease. On the other hand, the presence of cardiac disease carries a much more ominous prognosis.

A. History. In order to address the above questions, a detailed history is required. The history is the most crucial component of the evaluation of syncope. Particular attention should be paid to the following points:

1. Events leading to syncope. A patient's activity and posture before the episode should be noted. An episode occurring in a supine position suggests either an arrhythmic etiology or seizure, and makes a neurally mediated etiology or orthostatic hypotension unlikely. Conversely, syncope occurring during prolonged standing is likely

TABLE 7.3 Conditions to be Distinguished from Syncope

Disorders Not Associated with Loss of Consciousness
Falls
Drop attacks
Disorders Associated with Loss of Consciousness
Psychogenic (may or may not have loss of consciousness)
Metabolic disorders
Hypoglycemia
Hypoxia
Hyperventilation with hypocapnia
Epilepsy
Medication/pharmacologic (anesthetic/sedating including recreational drugs, alcohol)

TABLE 7.4 Typical Features of Vasovagal Syncope, Seizure, and Cardiac Syncope

	Vasovagal	Seizure	Cardiac
Feature onset	Subacute onset	Sudden onset or brief aura	Sudden onset
	Prodromal weakness, nausea	Auditory hallucinations or visual changes	None, chest pain, dyspnea, palpitations diaphoresis, and other cardiac symptoms may be present
Typical milieu or precipitating factor	Fatigue	Spontaneous onset	Often spontaneous onset
	Delayed prolonged standing meals	Triggered by flashing light or monotonous sensory stimulation	During or following exertion
	Crowded enclosed confines pregnancy pain or trauma emotional situation		Known or suspected structural heart disease
Posture at the time of onset	Standing or sitting	Standing, sitting, or supine	Standing, sitting, or supine
Appearance	Pallor	Normal or cyanotic Stertorous respiration	Pallor transient loss of awareness
	Brief tonic–clonic motor activity possible	Stereotypic motor activity	Brief periods of tonic–clonic motor activity possible
	Occasional urinary incontinence	Urinary incontinence common	Urinary incontinence uncommon
Residual	Rapid recovery	Delayed recovery	Rapid or briefly delayed recovery
	Recurrence with resumption of upright posture possible	Postictal cognitive impairment	If prolonged hypoxia, evidence of central nervous injury present system
		Todd's paralysis	Symptoms of cardiac dysfunction

neurocardiogenic. Vasovagal syncope should be suspected if the event was triggered by fear, pain, emotional distress, or instrumentation.

Syncope that occurs after rising from a supine or sitting position is consistent with orthostatic hypotension. Syncope occurring during or immediately after urination, defecation, coughing, or swallowing is a feature of situational syncope. Postprandial syncope is characterized by episodes that occur 15 to 90 minutes following meals. Syncope in the setting of neck manipulation such as extension, flexion, rotation, or compression (e.g., a tight shirt collar, necktie, or during shaving) may suggest carotid sinus hypersensitivity.

Syncope in the setting of exercise is particularly worrisome for a cardiac etiology. Syncope during physical exertion is a characteristic finding in aortic stenosis, atrioventricular (AV) block, or tachyarrhythmias, whereas loss of consciousness after exercise should arouse suspicion for hypertrophic cardiomyopathy or ventricular arrhythmia.

2. **Prodromal signs and symptoms** often provide clinically relevant information. Very brief prodromal symptoms lasting only seconds are a characteristic of cardiac causes, situational syncope, and orthostatic hypotension. Cardiac causes of syncope often do not have any prodromal symptoms or may present with dizziness and/or palpitations. On the other hand, vasovagal syncope typically has a more sustained warning period accompanied by symptoms of nausea, diaphoresis, and flushing. Focal neurologic symptoms such as vertigo, diplopia, ataxia, dysarthria, hemiparesis, and unilateral numbness may be indicative of a TIA as the cause of the loss of consciousness.
3. **Events during the syncopal period.** Obtaining as much detail as possible from witnesses regarding the events during the syncopal episode may be highly valuable. The patient may be amnestic for events before, during, and after the episode. A detailed history confirming the presence of true loss of consciousness and describing neuromuscular activity is extremely important. Although prolonged episodes of cerebral anoxia (more than 10–15 seconds) can induce brief involuntary motor activity, the presence of more sustained episodes of alternating tonic and clonic muscle action is strongly suggestive of a seizure. Urinary incontinence is more frequent among patients with seizure, although it can accompany syncope of any cause. Fecal incontinence is more specific for seizures.
4. **Postsyncopal events.** Details of events immediately following the loss of consciousness may provide important diagnostic clues. This history may also need to be obtained from witnesses. Prolonged duration of confusion, amnesia, or lethargy is more consistent with seizure activity rather than a cardiac or neurally mediated event. Similarly, the presence of focal neurologic symptoms or signs point to an inciting neurologic event such as a seizure with residual functional deficit (Todd's paralysis) or ischemic injury. Facial pallor points to syncope, facial plethora is more suggestive of seizure, and diffuse muscle soreness suggests seizure activity (see Chapter 6).
5. **Family history.** A family history of syncope, arrhythmias, or early sudden cardiac death may point to a genetic condition linked to ventricular arrhythmias, even in the absence of structural heart disease. Such a history should prompt more detailed cardiac investigation.
6. **Comorbid conditions.** The most important prognostic factor in patients presenting with syncope is the presence of cardiac disease. Thus, special emphasis should be placed on obtaining a detailed history of any cardiovascular pathology such as coronary artery disease, hypertension, CHF, hypertrophic obstructive cardiomyopathy, and valvular disorders. Symptoms associated with cardiac conditions such as palpitations, dyspnea, fluid retention, decreased exercise tolerance, lightheadedness, or chest pain require further workup.

The medical history should address the possibility of neurologic disorders predisposing to seizures mimicking syncope. This includes primary or metastatic neoplasia, as well as a history of previous trauma, infection, ischemic, or hemorrhagic injury to the brain. Medical conditions such as diabetes mellitus, alcohol abuse, vitamin B_{12} deficiency, or other metabolic disorders are associated with peripheral or autonomic neuropathy and can cause orthostatic hypotension.

A brief gynecologic history should be elicited to identify risk factors for pregnancy, particularly in ectopic locations. Pregnant patients are at increased risk for syncope due

TABLE 7.5 Agents Causing or Exacerbating Orthostatic Hypotension

ACE-Is
ARBs
Alpha-blockers
Beta-blockers
Calcium channel blockers
Nitrates
Sildenafil citrate
Phenothiazines
Opiates
Tricyclic antidepressants
Ethanol
Bromocriptine

Abbreviations: ACE-Is, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

to orthostatic hypotension and vasovagal reactions. Moreover, a ruptured ectopic pregnancy occasionally manifests with syncope.

A history of anxiety disorders and depression is important to elucidate. Psychiatric illness should be suspected as a potential etiology, especially in patients with severe, atypical, repetitive, and drug-refractory episodes. Patients with psychogenic syncope may have reproducible symptoms on tilt-table testing despite a normal heart rate, blood pressure, and EEG.

Finally, careful review of the patient's medication list is essential. Antihypertensive and other drugs can cause syncope by reducing cardiac output and lowering peripheral vascular resistance. As shown in Table 7.5, many psychotropic and antihypertensive medications can induce orthostatic hypotension. Drugs that prolong the QT interval may also present with syncope.

B. Physical examination.

1. Vital signs should include an assessment of orthostatic hypotension, which is defined as a decrease of 20-mm Hg in systolic pressure or 10-mm Hg in diastolic pressure following standing from a supine position. It is important that the supine blood pressure be obtained after at least 5 minutes of recumbency and the standing blood pressure measured initially and again after the patient has been erect for at least 2 minutes.
2. Given the prognostic importance of cardiac disease, a detailed cardiovascular examination should be performed. Palpation of the carotid arteries may demonstrate pulsus parvus et tardus (weak and delayed carotid pulsation), which occurs with hemodynamically significant aortic stenosis, or pulsus bisferiens (biphasic carotid pulsation), which may be found in hypertrophic obstructive cardiomyopathy. Similarly, particular attention should be paid to the presence of systolic-crescendo-decrescendo murmurs, implying the presence of aortic stenosis or hypertrophic obstructive cardiomyopathy. Peripheral edema, elevated jugular venous pressure, pulmonary crackles, hepatomegaly, and a third heart sound (S_3) signify heart failure. The presence of a carotid bruit signifies a high likelihood of diffuse atherosclerotic vascular disease involving the cerebral, coronary, and peripheral vasculature. A supraclavicular bruit and a diminished upper extremity arterial pulsation are evidence of subclavian steal syndrome.

   If carotid sinus supersensitivity is suspected, carotid massage can be performed in the absence of a bruit or known atheromatous disease. Carotid sinus hypersensitivity can be detected by means of monitoring changes in blood pressure and heart rate after 5 to 30 seconds of unilateral carotid artery massage. Responses are characterized as cardioinhibitory, vasodepressor, or mixed. Carotid sinus hypersensitivity is more common in older patients. Electrocardiographic and resuscitation equipment should be available.
3. A screening neurologic examination should be pursued to detect postictal cognitive impairment, the presence of focal neurologic defects indicative of either acute neurologic injury or a preexisting substrate for a seizure disorder, peripheral neuropathy that would predispose to orthostatic hypotension, or a movement disorder that would cause nonsyncopal falls.
4. A digital rectal examination should be considered if there is concern about gastrointestinal bleeding.

C. Laboratory studies.

1. **ECG.**
   a. Although it carries a low diagnostic yield, the resting 12-lead ECG is an important test for both prognosis and triage. Although it is relatively uncommon for the snapshot in time that the ECG is taken to demonstrate a culprit arrhythmia, the presence of pathologic Q waves, left axis deviation, left bundle branch block, or left ventricular hypertrophy may point to underlying cardiac pathology. Severe sinus bradycardia or AV block may be diagnostic.

      Repolarization abnormalities also may provide clues to the etiology of the syncope. These include a long QT interval (long QT syndrome), epsilon wave and precordial T-wave inversions (arrhythmogenic right ventricular dysplasia/cardiomyopathy), and right bundle branch block with saddle back ST elevation in leads V1–V3 (Brugada's syndrome). Other ECG signs of right heart strain ($S_1Q_3T_3$ or right bundle branch block pattern) suggest pulmonary embolism.

   b. **Ambulatory ECG**. Patients with recurrent episodes may benefit from ambulatory ECG. This should generally be performed in patients with no significant structural heart disease in whom an arrhythmia is either suspected or needs to be ruled out. Several types of monitors could be used, depending on the frequency of the symptoms: 24-hour continuous recordings, patient-activated looping and nonlooping event monitors that can be worn up to a period of 4 weeks, continuous 24-hour monitors that can also be worn for 4 weeks, and subcutaneous implantable loop recorders for long-term monitoring. Sensitivity and optimal recording duration are dependent on the frequency of events.

      Ambulatory monitoring has limited specificity because certain rhythm disturbances, such as brief pauses, premature atrial and ventricular contractions, and nonsustained ventricular tachycardia, can be detected even when they are not responsible for the syncope. Thus, it is important to correlate the findings of ambulatory monitoring with symptoms. If symptoms occur during monitoring and no ECG abnormalities are detected, a rhythm disturbance is effectively excluded as an etiologic factor.

2. **Echocardiography** is a powerful tool that should be commonly used when disease cardiac cause is suspected clinically. It can provide clues regarding the etiology of syncope such as valvular heart disease or atrial myxoma. More importantly, it can confirm or exclude the presence of left ventricular dysfunction, which is associated with a risk of sudden cardiac death and which carries important prognostic implications.
3. **Blood laboratory testing**. Serum electrolyte abnormalities should be excluded. Elevated prolactin levels have been reported in some patients hours after generalized tonic–clonic seizures. The same is true for creatine kinase levels, although increased serum concentrations can also be caused by injury during a syncopal episode. Serum glucose levels are most valuable at the time of the event, particularly in the evaluation of diabetic patients who have recently increased their insulin or oral hypoglycemic therapy or decreased their caloric intake. A complete blood count is occasionally helpful if blood loss or severe anemia is suspected.

   Arterial blood gas analysis can be useful in the evaluation of the occasional patient in whom pulmonary embolism is suspected because of the history, physical examination findings, or ECG results.
4. **Stress testing or coronary angiography** to assess for coronary ischemia is appropriate in some patients, particularly the elderly, those with exertional symptoms (syncope, chest pain, or dyspnea), cardiomyopathy, or ventricular arrhythmias.
5. **Electrophysiologic testing** is used to assess the integrity of the sinus node, cardiac conduction system, as well as the predisposition to ventricular and supraventricular arrhythmias. However, sensitivity is limited. The results are most often abnormal in patients with known heart disease or those with significant abnormalities on a routine ECG. Findings of greatest diagnostic value include inducible monomorphic ventricular tachycardia, markedly abnormal sinus node recovery times, inducible supraventricular tachycardia with hypotension, significant infra-Hisian disease, and pacing-induced infra-Hisian block. Recent studies have shown that patients with underlying left ventricular dysfunction are at high risk for arrhythmic death and benefit from prophylactic

defibrillator insertion even in the absence of syncope. Thus, patients with syncope and left ventricular dysfunction may not necessarily benefit from electrophysiological testing to assess inducibility of ventricular arrhythmias.

6. **Tilt-table testing**. The utility of tilt-table testing for the diagnosis of neurocardiogenic syncope remains poorly defined. It is only a moderately sensitive and specific test. A positive result is reproducible only 70% of the time. The limited reproducibility of the test and the variable natural history of unexplained syncope reduce its utility. Abnormal response patterns to tilt-table testing include the vasovagal response, which consists of a decrease in blood pressure (vasodepressor) and bradycardia (cardioinhibitory), and the dysautonomic response, which represents a failure of the autonomic system to compensate for an acute decrease in venous return that occurs with upright posture. Thus, the heart rate does not significantly change while the blood pressure declines. A third response to tilt-table testing is the postural orthostatic tachycardia response in which there is a significant increase in heart rate in response to upright positioning.
7. **Radiographic studies.** Routine CT and MRI of the brain have low yields but may be useful in the evaluation of patients who have sustained major head trauma, have a newly diagnosed seizure disorder, or have focal deficits on the neurologic examination.
8. **Electroencephalography** is not required routinely, but should be performed when clinical evaluation points to seizure or in syncope of undetermined etiology when there is adequate suspicion.
9. **Device interrogation.** Patients with implanted pacemakers or ICDs should have the devices checked by appropriate personnel. Not only should device malfunction be excluded as a cause of syncope, but modern devices store a plethora of diagnostic information that may be useful in diagnosis.

III. DIAGNOSTIC APPROACH

The majority of syncope is of cardiovascular cause, and the diagnosis often is suggested after a complete history and physical examination. In a new patient without prior evaluation, in addition to establishing the etiology when possible, a primary goal is defining whether the patient is at increased risk for mortality, particularly sudden cardiac death. Some patients with life threatening cardiac disorders may be otherwise asymptomatic. For example highly functional athletes, including at the professional level, may have malignant conditions (hypertrophic cardiomyopathy, genetic causes of ventricular arrhythmias, etc.) that lead to sudden cardiac death.

If the cause is unclear, evaluation of a resting 12-lead ECG should be performed in nearly all patients. Patients with symptoms or signs of cardiac disease, or those with abrupt syncope without warning should receive more detailed cardiac evaluation, which often includes echocardiography, evaluation for coronary artery disease, and referral to a cardiologist or electrophysiologist. Further cardiac testing, including electrophysiological studies and/or long-term cardiac monitoring, may be appropriate. Patients with unexplained syncope at high risk may be appropriate for preventive therapies, including the implantation of cardiac rhythm devices. Those with likely neurocardiogenic syncope should be treated for that disease. If needed, tilt-table testing could be performed to confirm the diagnosis. When the symptoms are deemed not to be of cardiovascular etiology or are nonsyncopal (e.g., seizure, psychogenic, traumatic, etc.), the patient should be managed accordingly or referred to the appropriate specialist.

Recommended Readings

Brignole M. Diagnosis and treatment of syncope. *Heart.* 2007;93:130–136.

Brignole M, Albani P, Benditt D, et al. Guideline on management (diagnosis and treatment) of syncope. *Eur Heart J.* 2004;25:2054–2072.

Fenton AM, Hammill SC, Rea RF, et al. Vasovagal syncope. *Ann Intern Med.* 2000;9:714–725.

Grubb BP, Kosinski D. Dysautonomic and reflex syncope syndromes. *Cardiol Clin.* 1997;15:257–268.

Kapoor WN. Syncope. *N Engl J Med.* 2000;25:1856–1862.

Middlekauff HR, Stevenson WG, Stevenson LW, et al. Syncope in advanced heart failure: high risk of sudden death regardless of origin of syncope. *J Am Coll Cardiol.* 1993;21:110–116.

Moss AJ, Zareba W, Hall J, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002; 346:877–883.

Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009) (Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology [ESC]; European Heart Rhythm Association [EHRA]; Heart Failure Association [HFA]; Heart Rhythm Society [HRS]). *Eur Heart J.* 2009;30(21):2631–2671.

Olshansky B, Poole JE, Johnson G, et al. Syncope predicts the outcome of cardiomyopathy patients: analysis of the SCD-HeFT study. *J Am Coll Cardiol*. 2008;51(13):1277–1282.

Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med.* 2002;347:878–885.

Zaidi A, Clough P, Cooper P, et al. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol.* 2000;36:181–184.

CHAPTER

8

Approach to the Patient with Gait Disturbances and Recurrent Falls

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Locomotor disturbances are common in all age groups but are particularly common among older people. Impaired locomotion is a source of disability for approximately 15% of people older than 65 years, rivaling dementia as the leading form of neurologic impairment. The examination of gait and balance provides the clinician with invaluable insight into a patient's functional status and is arguably the highest yielding component of the motor exam.

I. PATHOPHYSIOLOGY

A. Locomotion requires the integrated control of posture and movement. Postural control is necessary for static and dynamic stability during stance and locomotion. Somatic, visual, and vestibular sensory information are used in complex feedback (reflex) pathways that enable the nervous system to respond to altered stability. These sensory inputs are also combined with experience to adjust the pattern of stance or locomotion in anticipation of threatened stability. This anticipatory or **feedforward control of movement** is critically important because reflex responses are too slow and inaccurate for normal locomotion. Feedforward locomotor control utilizes working memory and other cognitive functions that are impaired in many patients with cerebral disease.

B. Anatomy and physiology. The basic locomotor rhythm emerges from spinal neuronal networks that interact directly with several brainstem nuclei and the cerebellum (Fig. 8.1).

1. **Cortical–basal ganglia–thalamocortical circuits** play an important role in selecting desired postures, movements, and behaviors while suppressing undesired postures, movements, and behaviors. Damage to these circuits impedes adaptation of gait and posture to varying environmental and emotional circumstances.
2. The **midbrain locomotor region** of the dorsolateral midbrain contains a heterogeneous group of neurons that connect with the basal ganglia and with raphe and reticular nuclei in the caudal pons and rostral medulla. The midbrain locomotor region and its connections play a critical role in the initiation of gait and control of posture.
3. The **cerebellum** interacts with pontomedullary reticular nuclei, the red nucleus, and the vestibular nuclei in the coordination of posture and rhythmic limb motion. It receives input from the spinal locomotor network; from peripheral somatosensory, vestibular, and visual pathways; and from cerebral cortex by way of the pontine, olivary, and other brainstem nuclei. These connections enable the cerebellum to play a pivotal role in the feedback and feedforward control of posture and movement.
4. The reticulospinal and vestibulospinal pathways in the ventral **spinal cord** are necessary for rudimentary control of the spinal networks. The corticospinal pathways are needed for flexible, adaptive control, and this "highest level control" is accomplished through rich cortical connections with the basal ganglia, thalamus, and cerebellum. Thus, the nervous system can modify posture and locomotion as dictated by environmental constraints, body mechanics, and personal desires.

II. ETIOLOGY

A. Gait disturbances. A disturbance of locomotion can occur at any level of the neuraxis (Fig. 8.1), and neurologic disturbances commonly lead to secondary skeletal deformities and muscle deconditioning that cause additional impairment of locomotion. The causes

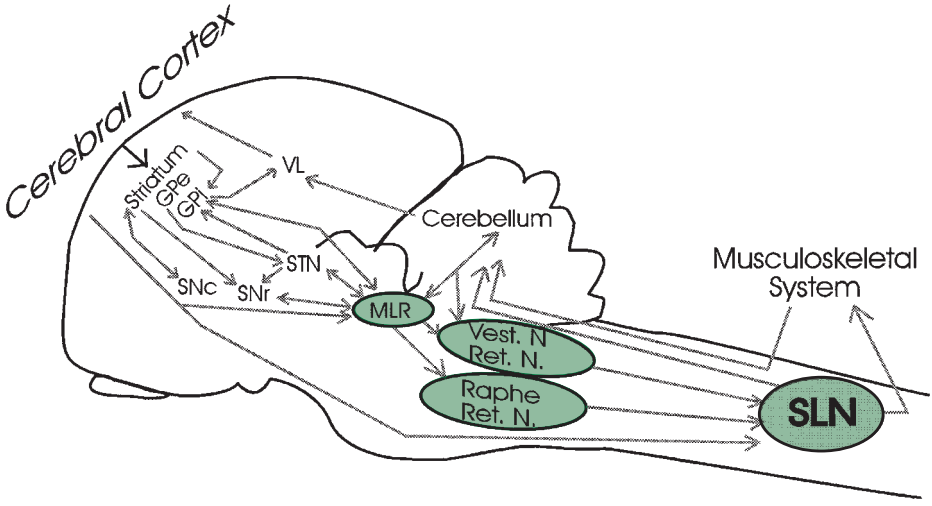

FIGURE 8.1 Schematic of the principal neural pathways of locomotor control. *GPe* and *GPi*, globus pallidus externa and interna; *VL*, ventrolateral thalamus; *SNc* and *SNr*, substantia nigra pars compacta and reticulata; *STN*, subthalamus; *MLR*, midbrain locomotor region; *Vest. N.*, lateral vestibular nucleus; *Ret. N.*, pontomedullary reticular nuclei; *SLN*, spinal locomotor network (central pattern generator).

of locomotor impairment are myriad. Multiple coexistent etiologic factors are common, particularly in older persons.

1. Gait disturbances are caused by any disease affecting the frontal and parietal lobes, basal ganglia, thalamus, brainstem motor nuclei, cerebellum, spinal cord, peripheral nerves, vision, vestibular function, and the musculoskeletal system.
2. Acute unilateral lesions typically produce focal neurologic signs and postural instability. The postural instability usually resolves or greatly improves with time.
3. Acute or chronic bilateral lesions typically produce a more severe and refractory disturbance of gait and balance.

B. Causes of recurrent falls. Environmental hazards and errors in judgment are responsible for 35% to 50% of falls in some studies, but most patients with recurrent falls have underlying neurologic disease. Common etiologies of recurrent falls include previous stroke, Parkinson's disease, severe arthritis, peripheral neuropathy, orthostatic hypotension, dementia (confusion), poor vision, and vestibular disease. Medications are also a common contributing factor or primary cause. Altered sensorium and impaired cognition impede feedforward modifications of posture and movement, resulting in increased risk of falls.

III. CLINICAL MANIFESTATIONS

A. Features of normal walking. The gait cycle is defined as the time between successive heel–floor contacts with the same foot (Fig. 8.2). One gait cycle consists of two steps (one stride). From right heel–floor contact to left toe-off is a period of double-limb support, which normally lasts approximately 10% of the total gait cycle. This phase of the cycle is followed by the left swing phase, which is simultaneous with and equal to the right single-limb support phase. The time from left heel–floor contact to right toe-off constitutes the second of two double-limb support phases in a gait cycle and is followed by the right swing phase and left single-limb support phase.

1. **Stride length (length of two successive steps) and cadence (steps per minute)** determine the velocity of walking (stride length × cadence ÷ 2). The magnitudes of arm swing, toe-floor clearance, and hip and knee rotations are proportional to stride

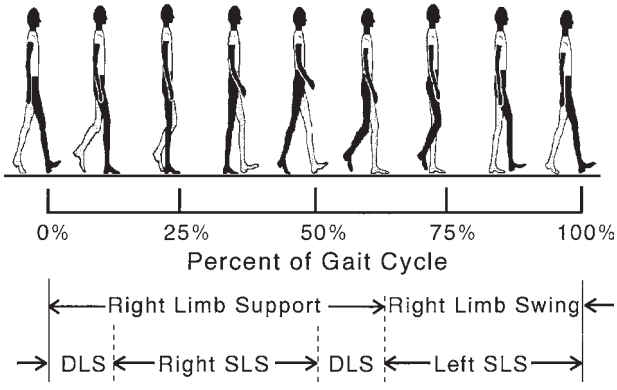

FIGURE 8.2 Phases of the normal gait cycle, expressed as percentage of total stride. *DLS*, double-limb support; *SLS*, single-limb support.

length and velocity, whereas the percentage time in double-limb support increases with reductions in gait velocity. Reduced gait velocity is a nonspecific sign of an underlying medical condition and is associated with reduced long-term survival.

2. **The total-body center of mass** oscillates vertically at a frequency equal to the cadence and horizontally at one-half the cadence. During a gait cycle, the two maxima in vertical oscillation occur in the middle of right and left single-limb support, and the two minima occur in the middle of the two phases of double-limb support. The left- and right-most horizontal excursions of the center of gravity occur at the times of mid-left and -right single-limb support. These vertical and horizontal excursions of the center of mass are optimized in such a way that the center of mass (body) moves forward with the least amount of expended energy. Consequently, most gait disturbances increase expended energy.

B. Normal development of walking. Most children walk independently by 15 months, and a fairly mature pattern of lower limb movement is achieved 3 months after walking begins. Maturation of gait and balance probably continues throughout childhood, but most of this maturation is accomplished by 3 or 4 years of age. At this age, most children have lost their lordotic posture and are capable of walking on narrow beams and standing with feet together and eyes closed. Failure to walk by 18 months should be investigated for neuromuscular disease, CNS pathology, visual impairment, and vestibular disease. Independent walking is delayed in blind children, only 50% walking by 24 months.

C. Abnormal patterns of walking. The characteristics of an abnormal gait are usually a mixture of primary abnormalities (direct effects of the underlying disease), secondary musculoskeletal abnormalities (e.g., joint contractures and musculoskeletal deconditioning), and compensatory changes. All must be considered when deciphering a patient's gait.

1. **Cautious gait** is a slow, guarded, or restrained pattern of walking that resembles someone walking on a slippery surface or in a threatening environment. There is slightly stooped posture (lowered center of gravity), reduced arm swing, increased time with both feet on the floor (double-limb support), slightly widened base, and reduced hip and knee rotations, all of which are commensurate with the patient's reduced stride and gait velocity. This pattern of walking is a nonspecific compensatory response produced by most causes of impaired locomotion, including cortical dementia (Alzheimer's disease). The features of cautious gait frequently dominate the clinical signs and symptoms of patients with mild neurologic impairment and provide the clinician with little clue to the underlying pathologic process.
2. **Dysequilibrium** is a disturbance of postural control and balance. Severe dysequilibrium produces a staggering, wide-based gait, particularly when the disturbance is acute. Mild or chronic dysequilibrium often is associated with a predominantly slow, cautious gait. Sudden or rapid movements (e.g., standing, turning, bending, and running) are avoided because they are destabilizing.

a. **Sensory dysequilibrium** occurs when there is a loss or conflict among vestibular, somatosensory, and primary visual pathways. Acute disturbances are more likely to produce falls, and disabling dysequilibrium generally does not persist unless at least two sensory modalities are impaired or unless there is concomitant impairment of the CNS. A cautious pattern of walking is typical among patients with isolated chronic peripheral visual, vestibular, or somatosensory deficits.
b. **Vestibular dysequilibrium** is associated with vertigo when the condition is acute. Patients with acute vestibular neuritis veer toward the side of the lesion and have horizontal nystagmus away from the lesion.
   (1) The **head impulse sign** is often positive with acute unilateral vestibular lesions. To elicit this sign, the patient is seated upright with the head positioned about 10° to one side. The patient is asked to fixate on the examiner's nose, and the examiner quickly rotates the patient's head 20° across the midline to the other side. When the head is rotated toward the side of a peripheral vestibular lesion, the eyes fail to rotate in the contralateral direction, due to the impaired vestibulo-ocular reflex. Consequently, head rotation is followed by a corrective saccade back to the examiner's nose. Normally, the eyes should remain fixated on the examiner's nose, resulting in no corrective saccade.
   (2) Nystagmus is typically unidirectional, away from the affected vestibular nerve, and is suppressed by visual fixation.
   (3) The Hallpike's maneuver should be performed in all patients with episodic vertigo, particularly if the vertigo occurs with head movement (e.g., lying down, rolling over in bed, looking up, and bending over) (see Chapter 16).
   (4) Patients are able to stand and walk without assistance, despite their vertigo.
c. **Somatosensory dysequilibrium** is most evident when the eyes are closed (Romberg's test) or otherwise impeded.
d. **Visual dysequilibrium** may occur when vision is acutely distorted with new glasses.
e. **Dysequilibrium due to lesions in the CNS** can cause profound loss of balance despite normal sensory feedback. Acute unilateral frontal lobe lesions cause patients to fall away from the side of the lesion. This dysequilibrium usually improves with time. Bilateral frontal lobe damage frequently causes more profound and sustained dysequilibrium due to inappropriate postural synergies. Patients lean the wrong direction in such a way that stability and locomotion are impeded. For example, patients may lean backward when being helped from a chair, or they may lean away from the pivot foot when attempting to turn. The patient's rescue response to the pull test is absent or greatly reduced, resulting in a backward fall or retropulsion.
   (1) To perform the **pull test**, the patient assumes a normal stance, and the patient is instructed to take a step, if necessary, to prevent falling. The examiner then briskly pulls the patient backward at the shoulders, hard enough to pull the patient off balance. The examiner should stand far enough behind the patient to provide the patient adequate room to regain balance. The test is abnormal if the patient takes more than one or two steps to regain balance. The examiner must catch the patient, if necessary, to prevent a fall. The test should be done with a wall behind the examiner, providing the examiner with support if needed.
   (2) The pull test is an examination of the rescue response. It is not a test of balance or static stability. The pull test is not valid unless the patient is pulled off balance, necessitating a rescue response by the patient.
f. **Subcortical dysequilibrium** occurs with lesions in the basal ganglia, ventrolateral thalamus, or dorsolateral midbrain (midbrain locomotor region; Fig. 8.1). Acute unilateral lesions cause a tendency to fall backward and laterally away from the lesion. With ischemic lesions, the dysequilibrium is temporary unless the damage is bilateral. Progressive supranuclear palsy produces bilateral destruction of these sites, so early impairment of balance is common in this disorder.
g. **Pusher syndrome** is produced by acute lesions in the ventrolateral thalamus and, less commonly, in the insula and post-central gyrus. Patients push themselves away from the lesion due to a misperception of body tilt toward the lesion.
h. **Vestibulocerebellar dysequilibrium** occurs with damage to the vestibulocerebellum and its brainstem connections. Patients tend to fall toward the side of the cerebellar

or central vestibular lesion. Damage to the vestibular nucleus can produce a sensation that the environment is tilted and that the body is being pulled toward the side of the lesion.

(1) The head impulse sign is negative in patients with central vestibulocerebellar lesions, except in rare patients with a lesion in the root entry zone of the vestibular nerve.
(2) These patients frequently are too unstable to walk without assistance.
(3) Nystagmus is multidirectional and depends on the direction of gaze.

3. **Start hesitation and freezing** are signs of akinesia. Patients move their extremities relatively normally while seated or recumbent, but their feet appear to stick to the floor while walking. Gait is often initiated with a few delayed, aborted, shuffling steps or is tricked into action by stepping over a self-imposed obstacle (e.g., the handle of an inverted cane) or by stepping onto a targeted spot on the floor. Environmental distractions and obstacles exacerbate start hesitation and elicit abrupt cessation of movement, called *freezing* (e.g., at a doorway).
4. **Short shuffling steps with en bloc turning** (marche á petits pas) are common among patients with damage to the frontal lobes and basal ganglia. Patients turn with multiple small shuffling steps and little or no rotational movement of the neck or torso.
   a. In idiopathic **Parkinson's disease**, there is an asymmetric reduction in arm swing, and the reduction in arm swing is greater than the reduction in stride. Steps are narrow-based, and posture is stooped. Pill-rolling hand tremor occurs frequently when patients walk or perform other locomotor tasks.
   b. Arm swing is increased in relation to the reduced stride of **lower-half parkinsonism**, and steps are wide-based. This pattern of walking may be seen in patients with multiple small infarcts and subcortical white matter degeneration in the basal ganglia and frontal lobes (Binswanger's disease) or in patients with other forms of atypical parkinsonism.
   c. **Festination of gait** is most commonly seen in Parkinson's disease. The steps become progressively shorter, the patient's forward lean increases, and the cadence may hasten as walking proceeds. Festination is commonly associated with start hesitation and freezing.
5. **Choreic gait** consists of extremity movements and postural shifts interrupted by sudden, variable flinging or dance-like movements (chorea) of the extremities and torso. Gait appears bizarre and hazardous. Huntington's disease is the most common etiology. Suppression of chorea with amantadine, tetrabenazine, or neuroleptic medications produces a disappointing improvement in gait when there are concomitant disturbances in postural control (subcortical or frontal dysequilibrium).
6. **Dystonic gait** is a variable pattern of walking in which extremity movements and postural shifts are interrupted by tonic or phasic co-contractions of antagonistic muscles in the limbs or torso. The limbs, trunk, and neck may be contorted into bizarre postures that depend on the relative strengths of muscle co-contraction. Dystonia can be focal or generalized and can emerge during a particular phase of the gait cycle (e.g., the swing phase). Dystonia may mysteriously disappear when walking backward.
7. **Hemiparetic gait** varies with the magnitude and distribution of weakness and spasticity. Reduced arm swing with flexor or dangling arm posture occurs in combination with a hyperextended lower extremity. Reduced hip and knee flexion and tonic ankle plantarflexion make foot-floor clearance during the swing phase of gait impossible unless the patient leans away from the hemiparetic limb and swings the spastic lower extremity outward and forward (**circumduction**). The toes scuff the floor, and the swing phase ends with the ball of the foot hitting the floor, instead of a normal heel strike. Patients with little spasticity and greater hip and knee mobility clear the floor during the swing phase with increased hip flexion.
8. **Spastic (paraplegic) gait** varies with the magnitude and distribution of weakness and spasticity in the lower extremities and also varies with the degree of sensory loss. Movement of the upper extremities depends on the level of the spinal cord lesion but is often relatively normal, even in patients with high cervical cord compression. Bilateral pyramidal tract dysfunction produces stiff, labored, scissoring movements of the hyperextended lower extremities, which are tightly adducted.

9. **Spastic diplegic gait** occurs among some patients with cerebral palsy and is caused by perinatal bilateral corticospinal tract damage. The knees and hips are excessively flexed during the gait cycle, and the tightly adducted hips cause the lower extremities to move in a scissoring, shuffling manner. The upper extremities and speech (pseudobulbar speech: slow labored speech) are usually much less affected than are the lower extremities, in contrast to bilateral hemiparesis and prominent pseudobulbar palsy in an adult. There is variable flexor posturing of the upper extremities and abduction of the arms.
10. **Cerebellar gait ataxia** occurs in patients with bilateral damage to the cerebellum. Gait is wide-based and reeling. Upper and lower limb movements are uncoordinated, and there is considerable stride-to-stride variability. Abnormal postural sway during quiet stance is present with eyes open and closed.
    a. Rostral vermian and paravermian damage produces a predominantly truncal and lower limb ataxia, with relative sparing of the upper body. This pattern of cerebellar degeneration is produced by chronic alcoholism and chronic thiamine deficiency.
    b. Caudal midline vestibulocerebellar damage produces dysequilibrium and eye movement abnormalities.
11. **Somatosensory ataxia** is exhibited by patients with large-fiber sensory polyneuropathy or posterior spinal column disease, with or without spinocerebellar tract damage. Somatosensory ataxia consists of wide-based, deliberate steps and postural dysequilibrium. Patients compensate for their loss of proprioception by watching their feet while walking. Postural sway is modest during quiet stance but increases markedly with eyes closed, due to the loss of proprioception (Romberg's sign). Thus, gait is more impaired in the dark or when vision is otherwise hindered. Somatosensory ataxia and steppage gait frequently coexist in patients with large-fiber sensorimotor polyneuropathy and in patients with degenerative disease that affects both the spinal cord and peripheral nerves (e.g., tabes dorsalis, vitamin B_{12} deficiency, Friedreich's ataxia, and hereditary dysmyelinating diseases).
12. **Spinal ataxia.** Disease of the spinal cord can cause somatosensory ataxia by affecting the dorsal columns. Lesions in the anterior columns produce an uncoordinated, dysrhythmic gait owing to impairment of the vestibulospinal and reticulospinal tracts. Furthermore, the ventral spinocerebellar tract is positioned in the anterolateral quadrant of the cord and provides feedback from the spinal locomotor network to the cerebellum. Thus, ataxia and dysequilibrium commonly coexist with spasticity in patients with spinal cord lesions and can dominate the clinical picture in some cases.
13. **Gait disturbances resulting from neuromuscular weakness.**
    a. **Waddling gait** is produced by muscle weakness in the hip girdle or, less commonly, by bilateral hip dislocations. Gait is wide-based and short-stepped. Increased lateral body sway occurs during the stance phase in compensation for weakness of the gluteus medius muscle. Increased arm abduction also may occur. Associated weakness in the paraspinal muscles produces exaggerated lumbar lordosis.
    b. **Steppage gait** is produced by distal symmetric motor polyneuropathy or bilateral peroneal neuropathy. Weakness of the ankle dorsiflexors interferes with foot-floor clearance during the swing phase of gait, so a compensatory increase in hip and knee flexion is necessary to raise the foot higher. Steps are high and short. The foot commonly slaps the floor at the end of swing phase. With polyneuropathy there is often coexistent weakness of ankle plantar flexion, which limits propulsion of the body at the end of the support phase.
14. **Antalgic gait.** Stance and gait are modified to reduce pain. Restricted (guarded) lower extremity and pelvic rotation occurs in locations dictated by the origin of pain. Limping is common.
15. **Hysterical gait.** Psychiatric gait disturbances are bizarre and variable. Patients frequently lean, lurch, and gyrate in a manner that requires good balance and coordination. Distracting the patient's attention or making the locomotor task more difficult tends to improve gait. For example, gait and stability increase when finger-to-nose testing is executed while the patient attempts to walk or stand. Gait also may improve when patients walk on their heels or toes. Tandem gait may initially seem impossible, but this task is frequently accomplished when attention is distracted with simultaneous performance of finger-to-nose testing, a difficult cognitive task (e.g., reciting the months of the year

backward), or both. *Be careful when making this diagnosis.* Dystonic gaits, choreatic gaits, and the gait disturbances of multiple sclerosis can be so bizarre that an erroneous diagnosis of psychiatric disease is made.

D. Systems classification of gait disorders. The clinical lexicon in **III.C.** provides no guide to the systematic evaluation of impaired mobility. A proposed classification scheme encourages clinicians to consider the entire neuraxis and neuromuscular system in deciphering a patient's gait. Gait disorders are classified as emerging from disturbances of the highest, middle, or lowest levels of motor control.

1. **Highest-level gait disorders** are caused by impairment of the cortical–basal ganglia–thalamocortical pathways. Unilateral lesions cause a tendency to fall away from the lesion. Bilateral lesions produce more profound disturbances of gait, seen in all forms of parkinsonism and most dementing illnesses. The characteristics of gait become increasingly bizarre and maladaptive as the underlying disease progresses. Examination while the patient is seated or recumbent may provide little clue to the characteristics and severity of impaired walking. Highest-level gait disorders in patients with bilateral pathology have one or more of the following characteristics.
   a. Absent or inappropriate corrective actions (rescue response) to postural perturbation (e.g., pull test). Patients often "fall like a log" or seem to make little attempt to rescue themselves. Corrective reactions may consist of inappropriate (counterproductive) limb movement or postural reactions such as leaning or propelling backward (retropulsion).
   b. Inappropriate or bizarre foot placement, postural synergy, and interaction with the environment (e.g., crossing the lower limbs while walking or turning; leaning toward the pivot foot when turning or leaning backward when attempting to rise from a chair or bed).
   c. Variable performance, influenced greatly by the environment and emotion. This variability can baffle caregivers unaware of this phenomenon.
   d. Hesitation and freezing, often when seemingly insignificant environmental objects or thresholds are encountered (e.g., a doorway).
2. In contrast to highest-level gait disorders, **lowest- and middle-level gait disorders** exhibit little or no change with alterations in environment, emotion, or cognitive activity. The clinical characteristics of lowest- and middle-level gait disorders are predictable from the neurologic or musculoskeletal deficits revealed during an examination while the patient is seated or recumbent. These characteristics do not change considerably during transitional movements from one steady-state posture or movement to another (e.g., when starting, stopping, and turning). Compensatory changes in gait are not inappropriate or maladaptive, rather they are simply limited by the underlying neurologic or musculoskeletal deficit.
   a. **Middle-level gait disorders** are caused by ascending or descending sensorimotor tract lesions, cerebellar ataxia, bradykinesia, hyperkinesia, and dystonia. Clinical subtypes are hemiparetic gait, spastic (paraplegic) gait, choreic gait, dystonic gait, spinal ataxia, and cerebellar ataxia.
   b. **Lowest-level gait disorders** are caused by disease of the muscles, peripheral nerves, skeleton, peripheral vestibular system, and anterior visual pathway. Also included are the effects of secondary muscle deconditioning (type II atrophy), limb contracture, spinal ankylosis, and reduced pelvic mobility, which are common among older persons.

IV. EVALUATION

A. History is critical in determining a specific cause and in identifying comorbidities that can adversely affect the patient's performance (e.g., cardiopulmonary disease, arthritis, glaucoma, macular degeneration, and painful feet).

1. **Functional disability** is largely determined with a careful history. The frequency and circumstances of falls and the ability to perform various activities of daily living (dressing, bathing, climbing stairs, and getting in and out of bed and chairs) are important measures of disability.

TABLE 8.1 Examination of Gait and Balance

Musculoskeletal assessment
Range of motion in spine, pelvis, hips, knees, and ankles
Muscle bulk, strength, and tone
Postural control and balance
Stability and posture while sitting and standing
Romberg's test
Rescue response (pull test)
Tandem walking
Hallpike's maneuver in patients with positional or episodic vertigo
Locomotion
Rising from a chair
Gait initiation
Walking (stride, arm swing, base, and symmetry of limb movement)
Turning and negotiating obstacles
Sitting

2. **Associated signs and symptoms** such as rest tremor (Parkinson's disease), oscillopsia and vertigo (vestibular or labyrinthine disease), urinary incontinence (frontal lobe lesions, hydrocephalus, and myelopathy), dementia, numb clumsy hands (high cervical cord lesion causing loss of dexterity, fine touch, vibration sensation, and proprioception), dysarthria and dysphagia (supraspinal lesion), and muscle wasting (peripheral neuromuscular disease) are helpful in making a diagnosis.

B. Physical examination is performed with the intent of localizing the lesion and establishing the degree of disability (Table 8.1). In patients with mild gait disorders, localizing signs may be subtle or largely shrouded by compensatory changes in gait (cautious gait). Clinicians must carefully search for localizing neurologic signs (e.g., rest tremor and pyramidal tract signs) and general physical signs (cardiopulmonary disease, poor visual acuity, and musculoskeletal disease) that provide clues to the underlying pathophysiology. Supine and standing blood pressure should be assessed in all patients with falls, even if there is no history of syncope.

C. Laboratory studies are useful in corroborating a diagnosis or deciphering a differential diagnosis derived from the history and physical examination.

1. A complete blood count and thyroid, renal, and liver function studies are performed in most cases. A vitamin B_{12} level is recommended in suspected subacute combined degeneration of the spinal cord and for elderly patients with a symmetric gait disturbance and cognitive or psychiatric symptoms.
2. Radiography of the hips, spine, and extremities are performed as needed. CT or MRI of the head or spine is needed if the signs and symptoms are not fully compatible with a peripheral disorder.
3. Electromyography and nerve conduction studies are helpful when neuromuscular disease is suspected.
4. Eye movement recordings (electronystagmogram-videonystagmography) may be helpful in differentiating Parkinson's disease from mild progressive supranuclear palsy.
5. Quantitative vestibular testing (electronystagmographic caloric testing) may be useful in distinguishing central from peripheral vestibular disorders. Peripheral vestibular disease may be associated with hearing loss that is only appreciated with audiologic examination.
6. Quantitative posturography and gait analysis with computed photogrammetric methods do not have an established role in the evaluation of most patients.

V. DIFFERENTIAL DIAGNOSIS

Differential diagnosis is particularly difficult in older persons with a roughly symmetric gait disturbance (Table 8.2).

TABLE 8.2 Differentiating the Neurologic Causes of Geriatric Gait Disturbances

Clinical Feature	Parkinson's Disease	Binswanger's Disease	NPH	PSP	MSA	Cervical Spondylosis
Reduced arm swing	++				+	
Asymmetric parkinsonism	++	+		+		
Pill-rolling rest tremor in the hands or rest tremor in the lower limbs	++					
Facial masking	++			+	+	
Good response to levodopa	++					
Postural instability and falls during the first year of symptoms		+	+	++	+	+
Prominent speech impairment during the first year of symptoms		+		++	++	
Stepwise progression		++				
Dementia in the first year or two of symptoms		++	+	++		
Subcortical white matter degeneration and microinfarcts		++				
Urinary dysfunction		+	++		+	+
Definite improvement after removal of 30–40 ml cerebrospinal fluid by means of lumbar puncture			++			
Hydrocephalus (>5.5 cm span across frontal horns)			++			
Supranuclear downward gaze palsy				++		
Ataxia				+	++	
Early symptomatic orthostatic hypotension					++	
Numb clumsy hands and Romberg's sign						++
Spastic lower limb movement						++
Spondylotic cervical spine and cord compression						++

+, suggestive; ++, highly suggestive.

NPH, normal pressure hydrocephalus; PSP, progressive supranuclear palsy.

VI. DIAGNOSTIC APPROACH

The **diagnostic approach** is to identify the primary cause of gait impairment and all contributing comorbidities. Many contributing illnesses are easily overlooked in the evaluation of patients with neurologic gait disturbances: vitamin B_{12} deficiency, hypothyroidism, depression, foot disorder (e.g., flat feet, painful feet, and clubfeet), muscle deconditioning, arthritic limbs, spinal deformities, cardiopulmonary disease, orthostatic hypotension, visual impairment, benign positional vertigo, and medications (e.g., sedative-hypnotics, antipsychotics, and metoclopramide). These contributing conditions are frequently more treatable than the primary neurologic illness.

VII. CRITERIA FOR DIAGNOSIS

Criteria for diagnosis are well established for most illnesses and depend heavily on the patient's history and physical findings.

A. The diagnoses of neurodegenerative diseases (e.g., Parkinsons, multiple system atrophy [MSA], and progressive supranuclear palsy) are based largely or entirely on the history and physical examination.

B. The diagnoses of other central and peripheral disturbances of gait disturbance are corroborated with neuroimaging or electrophysiologic studies, as needed.

C. The diagnosis of **idiopathic normal pressure hydrocephalus** (NPH) in older persons is particularly difficult. The clinical triad of gait disturbance, urinary incontinence, and cognitive dysfunction is not specific and also occurs in patients with vascular dementia, chronic subdural hematoma, and degenerative dementia. Unfortunately, there is still no fully reliable method for predicting the response to CSF shunting.

1. The cognitive dysfunction in NPH is a relatively mild and late component of the clinical triad.

2. Radiologic evidence of hydrocephalus (frontal horn span 0>5 cm; Evans' ratio 0.3) is necessary but does not guarantee a beneficial response to ventriculoperitoneal shunting of CSF.

3. Unequivocal improvement in gait after the removal of 30 to 40 ml of CSF by means of lumbar puncture supports the diagnosis but does not occur in all patients. Improvement after external lumbar CSF drainage for 3 days is more sensitive and specific but also more risky.

4. Improvement is achieved by approximately 50% of patients and sustained improvement by 30%. Complications occur in 20% of cases. Patients with an identifiable cause of hydrocephalus (e.g., aqueductal stenosis, Arnold–Chiari's malformation, and previous meningitis or subarachnoid hemorrhage) are more likely to respond than are those with idiopathic hydrocephalus. There are no randomized controlled trials.

VIII. REFERRAL

A. Neurologic consultation is recommended when the primary physician is uncertain or uncomfortable with the patient's diagnosis or treatment.

1. A second opinion is advisable before shunting a patient with presumed NPH and before operating on a patient with presumed cervical spondylosis.

2. Drug-resistant parkinsonism is strong evidence against the diagnosis of idiopathic Parkinson's disease.

B. Physical therapy and occupational therapy should be considered in most cases. An experienced occupational therapist, physical therapist, or visiting nurse can reduce falls and enhance mobility by performing a comprehensive safety evaluation of the patient's home. Handrails, raised toilet seats, adequate lighting, and rubber floor mats often are helpful. Elimination of electrical cords, clutter, and throw rugs throughout the home and repair of uneven floors and cracked sidewalks are additional considerations. Shoes

with slippery soles or high heels should be avoided. Properly prescribed walking aids frequently are useful and are best prescribed after a complete evaluation by a physical therapist.

C. Orthopedic and rheumatologic referrals should be considered when skeletal or foot abnormality impedes ambulation.

Recommended Readings

Bronstein AM. Vestibular reflexes and positional manoeuvres. *J Neurol Neurosurg Psychiatry*. 2003;74:289–293.

Elble RJ. Gait and dementia: moving beyond the notion of gait apraxia. J Neural Transm. 2007;114(10):1253–1258

Gallia GL, Rigamonti D, Williams MA. The diagnosis and treatment of idiopathic normal pressure hydrocephalus. *Nat Clin Pract Neurol*. 2006;2:375–381.

Hotson JR, Baloh RW. Acute vestibular syndrome. *N Engl J Med*. 1998;339:680–685.

Karnath HO. Pusher syndrome—a frequent but little-known disturbance of body orientation perception. *J Neurol*. 2007;254:415–424.

Lajoie Y, Teasdale N, Fleury M. Attentional demands for static and dynamic equilibrium. *Exp Brain Res*. 1993;97:139–144.

Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. *Neurology*. 1993;43:268–279.

Sudarsky L. Geriatrics: gait disorders in the elderly. *N Engl J Med*. 1990;322:1441–1446.

Sutherland DH. *Gait Disorders in Childhood and Adolescence*. Baltimore, MD: Williams & Wilkins; 1984.

Tinetti ME, Speechley M. Prevention of falls among the elderly. *N Engl J Med*. 1989;320:1055–1059.

CHAPTER

9 Approach to the Patient with Sleep Disorders

Mark Eric Dyken

This chapter focuses on primary sleep disorders described in the second edition of the *International Classification of Sleep Disorders* (*ICSD*). The greatest difficulties in approaching patients with sleep disorders often relates to an incomplete sleep history, as only a few diagnoses require formal polysomnography (PSG). Nevertheless, the patient usually cannot recall a pathologic event that occurs during sleep, and as such, an attempt to substantiate the sleep history with a bed partner, family member, or close associate should be made.

I. GENERAL APPROACH

A. The sleep history. What is the sleeping environment and bedtime routine? When is bedtime (regular or irregular)? What is the sleep latency (the time to fall asleep "after the head hits the pillow")? What is the sleep quality? Is it restful or restless and, if restless, why? How many arousals occur per night and for what reasons? What is the final awakening time? Is assistance in waking necessary? How does the patient feel on waking? How many hours of sleep are needed for refreshment? Does the patient nap, and, if so, how often, how long, and how does the person feel after the nap (refreshed, unchanged, and worse)? Does the patient experience excessive daytime sleepiness (EDS) or frank sleep attacks? A 2-week sleep diary, started prior to the initial clinic appointment, can diagnose disorders like inadequate sleep hygiene; a problem in 1% to 2% of adolescents and young adults, and in up to 10% of the sleep-clinic population that presents with insomnia (Fig. 9.1).

1. The degree of sleepiness can rate the severity of any sleep disorder through operational **definitions:** mild—sleepiness that impairs social or occupational performance during activities that require little attention (reading or watching television); moderate—sleepiness that impairs performance during activities that require some attention (meetings and concerts); and severe—sleepiness that impairs performance during activities that require active attention (conversing or driving).
2. **Subjective measure scales**, such as the Epworth Sleepiness Scale, can be used to qualify, quantify, and follow problems with sleepiness (Fig. 9.2). Chronically sleep-deprived persons can underestimate their sleepiness. Over time they lose the reference point from which to make comparisons and forget what it feels like to be fully rested. In such cases, excessive sleepiness can be reported as memory loss, slow mentation, and amnestic periods with automatic behavior.

B. The wake history. A history of insomnia and EDS can lead to, exacerbate, or result from a variety of medical and mental disorders, and from drug or substance use/abuse.

II. TYPES OF SLEEP DISORDERS

A. Insomnia. The *ICSD* criteria demand a history of difficulty initiating or maintaining sleep, or of waking up too early, or sleep that is chronically nonrestorative or poor in quality, and that the problem occurs despite adequate opportunity and circumstances for sleep. It also requires subsequent daytime impairment evidenced by at least one of the following: sleepiness, fatigue, malaise, impaired attention, concentration, or memory, social, vocational, or school dysfunction, tension, mood disturbance, reduced motivation, energy, or initiative reduction, errors or accidents at work or driving, headache, or gastrointestinal symptoms.

	Mon. a.m.	Tues. a.m.	Wed. a.m.	Thurs. a.m.	Fri. a.m.	Sat. a.m.	Sun. a.m.
1. What time did you go to bed last night?							
2. How many minutes did it take you to fall asleep?							
3. How many times did you wake up?							
4. How many total minutes did the awakenings keep you awake?							
5. What time did you wake up?							
6. What time did you get out of bed?							
Please use Wakefulness key below to answer the following questions:	**Mon. p.m.**	**Tues. p.m.**	**Wed. p.m.**	**Thurs. p.m.**	**Fri. p.m.**	**Sat. p.m.**	**Sun. p.m.**
1. How awake were you in the morning?							
2. How awake were you in the afternoon?							
3. How awake were you in the evening?							
4. Did you nap today? When and for how long?							

***Level of Wakefulness key:**

1 – Very sleepy
2 – Fairly sleepy
3 – Mix of sleepy and alert feelings
4 – Fairly alert
5 – Very alert

FIGURE 9.1 Example of a typical week-at-a-glance sleep diary.

1. **Adjustment (acute) insomnia**. This occurs in response to a clearly identifiable stressor and is expected to resolve when the stress ends or the patient adapts. Adjustment insomnia is often associated with anxiety and depression related to the specific stressor. The 1-year prevalence in adults is 15% to 20%, it is more common in women and older adults, and it may predispose to maladaptive behaviors and more persistent forms of insomnia.
2. **Psychophysiological insomnia**. This is a conditioned insomnia due to learned, sleep-preventing associations. It can represent persistent adjustment insomnia, where an external (or internal) stressor leads to a state of arousal "racing mind" in association with bedtime at home (patients often sleep better in the sleep lab; the "reverse first-night effect"). This affects 1% to 2% of the general population, is more frequent in women and adolescents, and is rare in children.
3. **Paradoxical insomnia.** Patients complain of severe insomnia with no objective evidence of disturbed sleep or daytime impairment. PSG studies show that these individuals overestimate their sleep latencies and underestimate their sleep times. Patient concerns are not alleviated when they are presented with these objective findings. High-frequency activity on EEG power-density measures may alter sleep perception in this

THE EPWORTH SLEEPINESS SCALE

Name: _____

Today's date: _____ Your age (years): _____

Your sex (male = M; female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze
1 = *slight* chance of dozing
2 = *moderate* change of dozing
3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in the traffic	_____

Thank you for your cooperation

FIGURE 9.2 The Epworth sleepiness scale. A score of 10 or greater suggests excessive daytime sleepiness. (With permission from Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14:540–545.)

patient population. Paradoxical insomnia occurs in <5% of insomniacs, is more common in women and young to middle-aged adults, and may be associated with neuroticism and depressive traits.

4. **Idiopathic insomnia.** This lifelong disorder is reported in 1% of young adults, begins in infancy or early childhood. It has no known precipitators or major psychological concomitants, but may be associated with attention deficit hyperactivity disorder (ADHD) and dyslexia. A genetic abnormality in sleep/wake mechanisms is suspected. PSG often shows reduced body movements despite severely disturbed sleep.
5. **Insomnia due to mental disorder, not due to substance or known physiological condition.** In this diagnosis, insomnia is a symptom of a mental disorder, but its severity demands treatment as a distinct problem, which often improves the underlying mental disorder. Major depression is frequently associated with insomnia and reduced rapid eye movement (REM) sleep latency, but PSG is not needed for diagnosis.
6. **Inadequate sleep hygiene.** This presents as a primary or secondary diagnosis in over 30% of sleep-clinic patients. It involves two categories of habits inconsistent with good sleep: practices that produce increased arousal (e.g., caffeine and nicotine use) and practices that are inconsistent with the principles of sleep organization (variable bedtime and awakening times). Important factors can include engaging in mentally or physically stimulating activities too close to bedtime and failure to maintain a comfortable sleeping environment.

7. **Behavioral insomnia of childhood.** There are 2 types seen in up to 30% of children (possibly more frequent in boys) after 6 months of age. Sleep-onset association type occurs with dependency on a specific stimulation, object, or setting for sleep. Sleep-onset associations are extremely prevalent and are only a disorder if highly problematic. Limit-setting type occurs with bedtime stalling, or refusal in toddlers and preschoolers. This problem is often due to poor practices of the caregiver.
8. **Insomnia due to drug or substance.** This is suppression or disruption of sleep during consumption; or exposure to a drug, food, or toxin; or upon its discontinuation. This affects 0.2% of the general population and 3.5% of those presenting to formal sleep-clinics. The PSG in chronic alcohol withdrawal can reveal light and fragmented sleep that may persist for years.
9. **Insomnia due to medical condition and physiological (organic) insomnia**. Disorders that cause discomfort (comfort is necessary for normal sleep) and neurodegenerative problems (with disruption of normal central sleep/wake mechanisms; poorly formed or absent sleep spindles are common) are representative of many possible etiologies. This diagnosis should only be considered when insomnia causes marked distress and warrants specific attention.

B. Sleep-related breathing disorders (SRBDs). In addition to the wake/sleep history, PSG is required in diagnosing SRBDs. PSG is the combined sleep monitoring of EEG, electromyography (EMG), electrooculography (EOG), and physiologic measures that include airflow, respiratory effort, and oxygen saturation (SaO_2). PSG differentiates four sleep stages—non-REM (NREM) stages N1, N2, and N3, and REM (stage R). An obstructive apnea is a drop in airflow by ≥90%, in association with continued inspiratory effort, for ≥10 seconds in adults, or the duration of 2 baseline breaths in children. A central apnea is an absence of inspiratory effort for ≥10 seconds in adults, or, in children, for 20 seconds, or the duration of 2 baseline breaths in association with an arousal, awakening, or a ≥3% SaO_2 reduction. A mixed apnea occurs when there is initially absent inspiratory effort, followed by resumption of inspiratory effort in the second part of the event. Hypopneas in adults occur with a ≥10 second period of reduced airflow of ≥30% or ≥50%, with respective SaO_2 reductions of ≥4% or ≥3% (or an associated arousal). In children, a hypopnea requires a ≥50% fall in airflow for a duration of 2 baseline breaths, in association with an arousal, awakening, or ≥3% SaO_2 reduction. Severity of a SRBD is suggested by the apnea–hypopnea index ([AHI]; the average number of apneas and hypopneas per hour of sleep). In adults, an AHI of 5 to 15 is considered mild; 15 to 30, moderate; and >30, severe.

1. **Central sleep apnea (CSA) syndromes.**
   a. **Primary CSA**. This idiopathic disorder is more frequent in middle aged to elderly males, associated with low normal waking $PaCO_2$ (<40 mm Hg), and high chemoresponsiveness (evidenced as central apneas) to the normal rise in $PaCO_2$ that occurs in sleep. It is significant when there are complaints of EDS, insomnia, or arousals with shortness of breath, and the PSG shows an AHI ≥ 5.
   b. **Cheyne–Stokes' breathing pattern (CSBP)**. PSG defines CSBP as at least 3 consecutive cycles of a cyclic crescendo and decrescendo change in breathing amplitude, with a central AHI of ≥5 and/or a cyclic crescendo and decrescendo change of ≥10 consecutive minutes. CSBP is most prominent in NREM sleep (usually absent or attenuated in REM). It occurs predominately in men >60 years of age, with a prevalence up to 45% in the congestive heart failure (CHF) population, and in 10% of strokes. CHF (a poor prognostic sign), stroke, and possibly renal failure are the most important precipitating factors.
   c. **High-altitude periodic breathing**. This is an acute response to a relatively rapid ascent to altitudes ≥4,000 m, where (usually the first night) there are recurrent central apneas in NREM sleep that alternate with hyperpneas in cycles of 12 to 34 seconds (often leading to frequent arousals with shortness of breath and EDS). This is considered a normal, and transient, adaptive phase to higher altitudes.
   d. **CSA due to medical condition (not Cheyne–Stokes) and due to drug or substance**. A majority of the medical conditions with CSA are associated with brainstem lesions, cardiac, or renal disorders. Regular use (>2 months) of long-acting opioids (methadone, time-release morphine, and hydrocodone), can lead to CSA (often in

association with obstruction, hypoventilation, and periodic breathing). The presumed etiology is from an effect on μ-receptors on the ventral surface of the medulla.

e. **Primary sleep apnea of infancy** (apnea of prematurity <37 weeks conceptual age, apnea of infancy ≥37 weeks, ≤1 year conceptual age). Central, mixed, obstructive apneas or hypopneas (most notably in active/REM sleep) associate with signs of physiologic compromise (hypoxemia, bradycardia, the need for resuscitative measures), but progressively decrease as the patient matures during the early weeks of life. The prevalence varies inversely with conceptual age (in 84% of infants <1,000 g, and <0.5% of full-term newborns), as it is related to developmental immaturity of brainstem respiratory centers. This has not been established as an independent risk factor for sudden infant death syndrome.

2. Obstructive sleep apnea (OSA) syndromes. OSA is associated with repeated episodes of upper airway obstruction. From 30 to 60 years of age, the prevalence ranges from 9% to 24% for men and 4% to 9% for women. Obstructions often result in oxygen desaturation, elevation in $PaCO_2$, and arousals, which disrupt sleep continuity and can lead to EDS. This syndrome often occurs among sleepy, middle-aged, overweight men with insomnia who snore. Premenopausal women are less commonly affected. This disorder also has been associated with systemic and pulmonary hypertension, nocturnal cardiac arrhythmia and angina, gastroesophageal reflux, nocturia, and an overall reduction in quality of life. Predisposing factors include familial tendencies, redundant pharyngeal tissue (e.g., adenotonsillar hypertrophy), craniofacial disorders (e.g., micrognathia, retrognathia, and nasal obstruction), endocrinopathy (e.g., acromegaly and hypothyroidism with myxedema), and neurologic disease.

a. **OSA, adult.**

(1) **History**. The patient or bed partner often reports restless, unrefreshing sleep and sleep maintenance insomnia with arousals associated with gasping, choking, or heroic snoring, possibly exacerbated by fatigue, alcohol, weight gain, or the supine sleeping position. Snoring may force the person to sleep alone and persist even when sitting. Although patients may not report daytime sleepiness, problems with fatigue, memory, and concentration are frequent. A family history of similar problems should be carefully sought.

(2) **Examination**. The blood pressure, body mass index (BMI = weight in kilograms per square meter of height) and neck and waist circumference should be documented, as hypertension and obesity may relate to OSA. Of general concern (following western standards) are a BMI ≥30 kg per m^2, a neck circumference of >40 cm, and a waist circumference (often measured at the iliac crest) >102 cm in men, and >88 cm in women. These are frequent signs in OSA that may predict comorbidities in the metabolic syndrome, heart disease, and stroke. Oral and nasopharyngeal patency and abnormalities of the tonsils, adenoids, tongue, soft and hard palate, uvula, nasal septum, turbinates, and temporomandibular joint as well as fatty infiltration of soft tissues in the upper airways should be documented.

(3) **PSG.** Recurrent obstructions often result in microarousals/arousals, which contribute to EDS (however, the frequency of events correlates poorly with sleepiness severity). Events generally appear worse in the supine position and during REM sleep. Tachy-brady cardiac arrhythmias and asystole may be documented. The diagnosis of OSA is considered with an AHI ≥5, when there is at least one symptom that may include EDS, insomnia, arousals with shortness of breath or choking, and witnessed loud snoring or apneas. The diagnosis can also be given with an AHI ≥15 in the absence of symptoms.

(4) **Differential diagnosis.** Loud snoring and respiratory effort related arousals (RERA), as part of the upper airway resistance syndrome (UARS), can lead to EDS with no PSG evidence of OSA (as RERA are pathophysiologically similar to obstructions). During PSG, defining RERA requires esophageal balloon (or nasal pressure/inductance plethysmography) monitoring that reveals ≥10 second episodes of, respectively, increasing negative pressure, or flattening of nasal pressure waveforms (that correspond to increased respiratory effort), which terminate with arousal.

(5) **Other tests**. In severe cases, an interdisciplinary approach may necessitate ECG, chest radiography, echocardiography, and pulmonary function tests (addressing pulmonary hypertension and right ventricular hypertrophy), cephalometric evaluations of the upper airways, and extensive cerebrovascular assessments.

b. **OSA, pediatric**. The prevalence of OSA is 2% in the general pediatric population, with girls and boys being affected equally, but with a higher prevalence in African American relative to Caucasian children. Some children may have OSA breathing patterns similar to adults, nevertheless, younger children may be prone to obstructive hypoventilation (long periods of persistent partial upper airway obstruction).
   (1) **History**. Snoring and difficulty breathing are common; often with reports of associated neck hyperextension and diaphoresis. Cognitive and behavioral complications (ADHD) are frequent, with EDS being reported especially in older children.
   (2) **Examination**. Children with OSA generally have relatively large tonsils and adenoids, and obesity is becoming more common. Pectus excavatum may result from chronic paradoxical respirations. Patients with craniofacial abnormalities, Down's syndrome, neuromuscular diseases, cerebral palsy, gastroesophageal reflux (with upper airway edema), mucopolysaccharidosis, sickle cell disease, or who are post cleft palate repair may be prone to OSA.
   (3) **PSG**. Even relatively short obstructions may lead to severe hypoxemia as children have faster respiratory rates with lower functional residual capacities than adults. OSA in children is defined by an AHI ≥1.
   (4) **Differential diagnosis**. In children UARS and RERA can be diagnosed when snoring (or noisy breathing, elevated end-tidal CO_2/transcutaneous PCO_2, or increased work of breathing) is associated with esophageal pressure monitoring that shows a progressive increased inspiratory effort, or the nasal pressure sensor amplitude falls <50% of baseline with waveform flattening, for a duration of at least 2 baseline breaths.

c. **Sleep-related hypoventilation/hypoxemia syndromes**. These syndromes often coexist with elements of OSA and CSA.
   (1) **PSG**. Hypoventilation appears as prolonged periods (often several minutes or longer) of reduced respiratory effort (shallow breathing) associated with sustained SaO_2 desaturations, with a ≥10 mm Hg increase in $PaCO_2$ (with an absolute value that is often >45 mm Hg) in comparison to awake supine values, in the relative absence of obstructive and central events. An arterial blood gas (ABG) that reveals an elevated $PaCO_2$ immediately upon awakening is suggestive of hypoventilation. Alternatives are being investigated as clinically it is impractical to obtain ABGs during sleep. Although there is presently insufficient evidence to allow specification of sensors, both end-tidal and transcutaneous CO_2 monitors can be used for surrogate measures of $PaCO_2$ if there is demonstration of reliability and validity within the testing laboratory.
      (a) **Sleep related nonobstructive alveolar hypoventilation, idiopathic.** Sleep related nonobstructive alveolar hypoventilation, idiopathic is postulated to result from a lesion of medullary chemoreceptors, leading to periods (often worse in REM sleep) of decreased tidal volume lasting several minutes with sustained SaO_2 desaturations and elevated carbon dioxide levels. This often presents in adolescents or young adults.
      (b) **Congenital central alveolar hypoventilation syndrome.** Similar to sleep related nonobstructive alveolar hypoventilation, idiopathic, the congenital central alveolar hypoventilation syndrome can lead to polycythemia, pulmonary hypertension, heart failure and death. It is a rare congenital genetic disease (most cases due to de novo mutations in the PHOX2B gene) associated with failure of automatic central control of breathing, usually evident at birth, and requiring intubation. Patients may progress to adequate waking breathing, although some need continuous ventilatory support. The congenital central alveolar hypoventilation is often associated with Hirschsprung's disease, autonomic dysfunction, neural tumors, dysphagia, and hypoventilation that may appear worse during slow wave (stage N3) sleep.

(c) **Sleep-related hypoventilation/hypoxemia due to pulmonary parenchymal or vascular pathology**. This occurs when disease has been documented using pulmonary function tests, radiography, echocardiography, pulmonary artery catheter measurements, and hemoglobin studies. Associated diseases include interstitial lung diseases, pulmonary hypertension, sickle cell anemia, and cystic fibrosis. Worse pulmonary function and a lower waking SaO_2 increases the risk for sleep hypoventilation/hypoxemia, and subsequent polycythemia and cardiac dysrhythmias. PSG findings are generally worse in REM sleep, and include an SaO_2 <90% for >30% of the total sleep time.

(d) **Sleep-related hypoventilation/hypoxemia due to lower airways obstruction**. This occurs in disorders with obstruction or increased airflow resistance below the larynx, such as chronic obstructive pulmonary disease ([COPD]; chronic bronchitis and emphysema), bronchiectasis, cystic fibrosis, and α-1 antitrypsin deficiency. The greatest risk factor for COPD (the third leading cause of death in the United States) is cigarette smoking. Patients with COPD and significant sleep hypoxemia have increased pulmonary hypertension and mortality. Lower airway obstructive disease is evidenced by a forced expiratory volume exhaled in 1-second per forced vital capacity ratio <70% of predicted values.

(e) **Sleep-related hypoventilation/hypoxemia due to neuromuscular and chest wall disorders**. Hypoventilation can occur from reduced contractility of the ventilatory musculature (intercostals, accessory muscles, and diaphragm) or due to anatomic distortion of the chest wall (which causes inefficient breathing). This often affects patients with obesity, amyotrophic lateral sclerosis, myasthenia gravis, muscular dystrophies, kyphoscoliosis, postpolio syndrome, and spinal cord injuries with diaphragmatic paralysis. The course of the breathing disturbance approximates the severity of the underlying condition and can put the patient at risk for pulmonary hypertension, cor pulmonale, and cognitive dysfunction.

C. Hypersomnias of central origin. These disorders involve dysfunction of the normal central wake/sleep centers. The ascending reticular activating system (ARAS) of the brainstem promotes wakefulness through two pathways, leading to diffuse cortical projections. A ventral hypothalamic system excites the lateral nucleus (LN) and tuberomammillary nucleus of the hypothalamus, which relays to cholinergic basal forebrain cells, whereas a dorsal thalamic route stimulates nonspecific midline and intralaminar nuclei, while inhibiting the reticular nucleus of the thalamus. The central sleep-onset system has a hypothalamic "sleep switch" in the preoptic area of the hypothalamus (the ventrolateral and median preoptic nuclei). These nuclei have reciprocal inhibitory relays with multiple waking centers.

1. **Narcolepsy**. Classically begins during puberty or young adulthood with excessive sleepiness. Sleep attacks can occur while driving, engaged in active conversation, or eating. Once sleepiness stabilizes, it generally does not progress, but the other symptoms associated with narcolepsy may come and go. Cataplexy, often precipitated by strong positive emotion, involves attacks that range from brief sensations of weakness to essential paralysis. The spells are transient and do not produce cognitive impairment. Hypnagogic (at sleep-onset) and hypnopompic (on awakening) hallucinations are generally frightening visual, auditory, or movement perceptions that essentially represent dreaming while awake. Sleep paralysis occurs during the transition from sleep to waking (or waking to sleep). The patient may experience brief paralysis (seconds to minutes) with the inability to speak. Other symptoms of narcolepsy can include insomnia, poor memory, depression, and automatic behaviors. Narcolepsy is associated with pathologic REM sleep mechanisms, clinically evidenced as sleepiness, cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations. These symptoms are due to a deficiency of wake-promoting neuropeptides (orexins/hypocretins) in the LN of the hypothalamus.
   a. **PSG and the multiple sleep latency test (MSLT)**. REM sleep is defined on PSG and MSLT as a "relatively low voltage, mixed frequency EEG" of alpha and theta waveforms, associated with "saw-tooth" waves, that occurs with an EOG that shows REMs and an EMG that documents atonia. In diagnosing narcolepsy, an MSLT

should be performed approximately 2 hours after the patient awakens from an overnight PSG (which assures adequate sleep and a paucity of other sleep disorders). The MSLT is a series of five 20-minute attempts at napping (during the patient's normal waking hours), which are separated by approximately 2-hour intervals. A mean sleep latency (the average time it takes the patient to fall asleep after the beginning of each individual nap period) ≤8 minutes and 2 or more naps during which REM sleep appears is classically associated with narcolepsy.

b. **Split-screen, video-PSG studies**. These studies, performed during cataplectic events precipitated by emotional provocation, have shown REM sleep patterns during periods when patients were able to give appropriate responses to detailed questioning. Similar results have been documented during episodes of sleep paralysis and hypnagogic hallucinations.

c. **Genetics**. Three percent of patients with idiopathic narcolepsy have a first-degree relative with excessive sleepiness and cataplexy, whereas 40% have at least 1 relative with excessive sleepiness. The major histocompatibility complex of chromosome 6 contains genetic markers for narcolepsy. In over 90% of patients with cataplexy, the mapping of specific human leukocyte class II antigens (DR2 and DQ1) reveal a subtype human leukocyte antigen allele DQB1*0602. The presence of the DQB1*0602 allele in only 40% of patients with 2 or more SOREMPS on MSLT indicates genetic testing alone is not sufficient for the diagnosis of narcolepsy.

d. **Orexins/hypocretins**. A paucity of these wake-promoting neuropeptides, located in the LN of the hypothalamus, may be the primary deficit in idiopathic narcolepsy. Low CSF levels (≤110 pg per ml or one-third of mean normal control values) are found in more than 90% of narcoleptics with cataplexy.

2. **Recurrent hypersomnia.**

a. **Kleine–Levin's syndrome (KLS)**. The KLS, classically more common in males, is characterized by periods of hypersomnia, hyperphagia, and encephalopathy that can last several weeks, recur up to 10 times a year, and generally improve over a 4-year period. The brain MRI is generally normal, but single photon emission computed tomography scans have shown reduced thalamic blood flow. Hypothalamic injury has been reported at autopsy and suggested by case reports associated with encephalitis, stroke, traumatic brain injury, and low CSF levels of orexin/hypocretin.

b. **Menstrual-related hypersomnia (MRH)**. MRH is associated with recurrent hypersomnolent episodes occurring within the first months after menarche. Episodes routinely last 1 week and resolve quickly after menses. A reported elevation in 5-hydroxyindolacetic acid turnover suggests that MRH is related to a hormone imbalance.

3. **Idiopathic hypersomnia (IH)**. The 2 variants of IH are either with or without long sleep time. Patients with long sleep time have prolonged, sustained nonrefreshing nocturnal sleep periods lasting 10 to 20 hours, whereas in IH without long sleep time, these periods are >6 hours, but <10 hours. An IH is a lifelong problem that begins early in life and has suspected genetic concomitants. This disorder is due to dysfunctional NREM sleep mechanisms, with NREM onset sleep periods, and difficulties in waking associated with sleep drunkenness. The autonomic concomitants implied by the frequency of associated migraine headaches, orthostasis, syncope, and Raynaud's syndrome suggest hypothalamic dysfunction. Nevertheless, CSF studies have shown normal orexin/hypocretin levels, with histamine deficiency.

4. **Behaviorally induced insufficient sleep syndrome**. This is due to voluntary, but unintentional, chronic sleep deprivation. Patients are preoccupied with etiologies they presume are responsible for their sleepiness (causes other than a reduced total sleep time), and their symptoms, which may include irritability, malaise, and reduced concentration.

5. **Hypersomnia due to a medical condition**. The conditions that can cause hypersomnia through direct effects on wake/sleep mechanisms include neurodegenerative disorders, brain trauma and tumors, encephalitis, genetic disease, and stroke. The diagnosis of narcolepsy due to medical condition is given when these conditions lead to cataplexy.

a. **Neurodegenerative disorders**. These can include Parkinson's disease, Alzheimer's disease (AD), and frontotemporal and Lewy's body dementia. In Parkinson's disease,

hypersomnia may result from degeneration of dopaminergic cells in the substantia nigra, and cholinergic neurons in the basal forebrain.

b. **Post-traumatic hypersomnia**. This type of hypersomnia has been reported even in mild head injury (without loss of consciousness) and also during recovery from post-traumatic coma (where early PSG return of sleep spindles and normal sleep–wake cycling is a positive prognostic sign).

c. **Genetic disorders.** Specific genetic disorders associated with hypersomnia include Norrie's disease, Niemann–Pick's type C disease, myotonic dystrophy, Prader–Willi's syndrome, fragile X syndrome, and Moebius' syndrome. In Niemann–Pick's disease type C, accumulation of unesterified cholesterol and sphingolipids in the hypothalamus, with a subsequent reduction in orexin/hypocretin, may be a cause of sleepiness. In myotonic dystrophy, hypothalamic (orexin/hypocretin) dysfunction, and loss of serotonin in the dorsal raphe nucleus, may account for hypersomnolence.

d. **Endocrine disorders.** Hypersomnia secondary to endocrine disorder is typified by hypothyroidism. A significant reduction in slow wave activity can be induced by hypothyroidism.

e. **Hypersomnia due to drug or substance.** This includes use, abuse, and cessation of stimulants and sedative-hypnotic drugs.

6. **Hypersomnia not due to substance or known physiological condition.** These are related to psychiatric conditions that include adjustment, personality, schizoaffective, mood, and seasonal affective disorders. Subtypes include hypersomnia associated with a major depressive episode (atypical depression and bipolar type II disorder) and conversion disorder (or as an undifferentiated somatoform disorder).

D. Circadian rhythm sleep disorders (CRSDs). A CRSD occurs when there are incongruities between the sleep–wake schedule demanded by society and the intrinsic sleep–wake pattern of the patient (determined in large part by the circadian pacemaker—the suprachiasmatic nuclei of the anterior hypothalamus). When not extrinsic or self-imposed ("jet lag" or shift work), these problems are believed to result from abnormal intrinsic physiologic responses to environmental time cues (*Zeitgebers*) such as sunlight (which exerts its effects through retinal–hypothalamic pathways). The patient's state of sleepiness or arousal subsequently is out of synchrony with that of the general population. The result is alternating sleepiness and insomnia when the patient tries to follow a normal schedule.

1. **History**. In many cases, a sleep log can be diagnostic. The accurate, 1- to 2-month documentation of all bedtimes, final awakening times, and nap times, can help differentiate a circadian rhythm disorder from poor sleep hygiene. The log should be filled out during a vacation or "free" time so as to avoid societal constraints that prevent the patient from following their intrinsic sleep–wake pattern.

2. **Other tests**. Actigraphy is a method for recording limb movement using a devise (usually placed on the wrist) that records movement. Digitized data are downloaded to a computer, and computer algorithms are used to approximate wake and sleep periods over prolonged periods of time. The American Academy of Sleep Medicine (AASM) indicates actigraphy is reliable and valid for detecting sleep in healthy populations and useful in the routine evaluation of CRSDs, insomnia, and EDS. In addition, some sleep disorder centers can monitor hormonal rhythms (such as dim-light melatonin onset) and 24-hour body temperature fluctuations, which can lose normal circadian fluctuations and amplitudes in CRSDs.

a. **CRSD, delayed sleep phase type**. This occurs with a prevalence rate up to 16%, and is primarily noted in adolescents and young adults, and individuals with evening type personalities (as defined by the Horne–Ostberg's questionnaire). There is an association with polymorphisms in the circadian clock gene hPer3, with a positive family history in 40%. Patients report chronically late bedtimes with late final awakening times (delayed over 2 hours relative to societal norms), which can be confirmed with a sleep logs and actigraphy (over at least 7 days). These individuals do not report sleepiness unless they attempt to follow the normal societal sleep–wake schedule.

b. **CRSD, advanced sleep phase type**. Persons with this syndrome go to sleep very early in relation to the setting of the sun, arise very early in relation to sunrise, and

do not report excessive sleepiness during their "normal" waking hours. This tendency increases with age, and has a prevalence of 1% in middle-aged and older adults. Almost all patients are considered morning type personalities. In younger patients genetic factors may be involved, possibly with an autosomal dominant inheritance pattern, in association with a mutation in the circadian clock gene hPer2. This CRSD is generally addressed only if it impairs the quality of the patient's work, social, or family life.

c. **CRSD, irregular sleep–wake type**. In this disorder, there is no definitive sleep–wake rhythm. Patients subsequently have intermittent nocturnal insomnia and variable periods of daytime sleepiness, which generally result in 3 or more irregularly timed naps during a 24-hour period. The total sleep time during a 24-hour is normal, but the timing of sleep is not predictable. This disorder is can be seen in the institutionalized elderly, in association with dementia, and in children with intellectual disabilities.

d. **CRSD, free-running type**. Also known as hypernychthemeral syndrome, these patients have an inability to synchronize (entrain) the physiologic desire for a sleep–wake schedule that is greater than 24 hours with a normal 24-hour day. Subsequently these patients continually "phase delay" and on a day-to-day basis show a progressive 1 to 2 hour delay of bedtime and final awakening times. When they attempt to keep regular sleep–wake schedules (fixed bedtime and final awakening times), they experience recurrent periods without sleep problems (when their intrinsic schedules match society's), which are then followed by the gradual onset of periods associated with sleep-onset insomnia, difficulty waking in the morning, and daytime sleepiness (when their intrinsic schedules are out of synchrony with society's). These patients are often blind and the disorder has been reported with intellectual disability, schizophrenia, and rarely in the otherwise normal population. Upon diagnosis, imaging studies of the brain can be considered, as this disorder has been associated with suprasellar lesions.

e. **CRSD, shift work type**. In this disorder, insomnia and EDS result when the patient works during the normal physiologic sleep period. The prevalence of shift work in industrialized countries is 20% and the estimated prevalence of insomnia/EDS due to shift work is 2% to 5%. This disorder may complicate gastrointestinal and cardiovascular disorders, cause social difficulties, or lead to drug dependency in attempts to improve sleep, and presents work-related safety concerns.

f. **CRSD, due to medical condition**. Degenerative diseases (including Parkinson's and AD), blindness, and hepatic encephalopathy can alter the function of the biologic clock and lead to insomnia and EDS. Sleep-related problems can then influence the severity of the underlying condition (e.g., "sun downing" and nocturnal wandering in dementia).

E. Parasomnias. These are undesired sleep-related physical events, associated with semipurposeful behaviors and elevated autonomic activity. Of the parasomnias, only the REM sleep behavior disorder (RBD) requires PSG for diagnosis.

1. **Disorders of arousal (from NREM sleep)**. Confusional arousals, sleepwalking, and sleep terrors are closely related parasomnias that can occur in a familial pattern, primarily among children, and generally begin in slow-wave (stage N3) sleep during the first third of the night. The spells are associated with general lack of environmental responsiveness, automatic actions, confusion, disorientation, and occasional injuries. After these events, from which the patient is generally unarousable, there usually is amnesia without dream recall.

a. **Confusional arousals**. These are prevalent in children (17.3% in children 3 to 13 years of age) and adults <35 years of age. Young children may sleepwalk when they become adolescents. Adolescents and adults can have the variants; severe morning sleep inertia, and sleep-related abnormal sexual behaviors. Severe morning sleep inertia is a persistent problem that can lead to sleep-related injury (risk of motor vehicle accidents), violent behavior, poor work performance, and social problems. Sleep-related abnormal sexual behaviors can lead to assaultive behaviors followed by morning amnesia.

b. **Sleepwalking.** This occurs with a prevalence up to 17% in children (peaking by 8 to 12 years of age) and in up to 4% of adults (with associated violent behaviors

occurring more frequently in men). The rate of familial sleepwalking is 60% when both parents are affected. Childhood sleepwalking can lead to injury, but usually resolves by puberty.

c. **Sleep terrors.** These occur with a prevalence rate up to 6.5% in children and in 2.2% of adults. Adults may have associated bipolar, depressive, or anxiety disorders. The onset is usually between 4 and 12 years with resolution often during puberty. During the spell, the patient often appears frightened, with tachycardia, tachypnea, diaphoresis, and inconsolable screaming and crying that can last from a few seconds to 20 minutes.

2. **Parasomnias usually associated with REM sleep.**

a. **REM sleep behavior disorder**. This disorder is associated with violent behavior during sleep that reflects dream enactment. Events begin during REM ("dreaming" or "paralyzed") sleep and are followed, after arousal, by reports of dream imagery compatible with the actions observed during the spell. This disorder generally appears after the age of 50 years, in elderly men, with a prevalence of 0.5% to 0.8% in the elderly population. It is often associated with synucleinopathies (neurodegenerative disorders like Parkinson's disease and Lewy's body dementia, which are associated with neuronal lesions from aggregates of insoluble α-synuclein protein), being reported in one-third of patients with newly diagnosed Parkinson's disease, and in 90% of patients with multiple system atrophy (MSA). The patients have histories of potentially harmful sleep-related body movements associated with dreaming. Patients frequently report sleep-related injuries, which include bruises, lacerations, dislocations, fractures, and subdural hemorrhage. The pathophysiology may be degeneration of REM-atonia pathways. The PSG shows that during REM sleep, muscle tone generally is elevated. Periodic limb movements during sleep (PLMS) are seen in 75% of patients during NREM sleep. Behaviors appearing as dream enactment may be appreciated during REM sleep.

(1) **Subtypes**. Preclinical RBD ("REM without atonia") may develop into clinical RBD in 25% of cases. Parasomnia overlap disorder occurs when RBD occurs with sleepwalking and/or sleep terrors. Status dissociatus is diagnosed when the PSG has no discernable sleep stages, but behaviors that resemble sleep and suggest dreaming and RBD. This can be seen with the prion disease fatal familial insomnia, with parkinsonism, dementia, and MSA.

F. Sleep-related movement disorders.

1. **Restless legs syndrome (RLS)**. RLS is clinically diagnosed by symptoms which form the acronym URGE; an urge to move the limbs (usually the legs), that is worse at rest, improves with movement (going), and is most evident in the evening (often when attempting to go to sleep). In children, there may be an association with ADHD. This symptom complex affects up to 10% of the general adult population, 30% of patients with rheumatoid arthritis, and up to 20% of patients with uremia (up to 62% of those on hemodialysis). It is reported almost twice as often in women, possibly related to the 11% to 20% prevalence recognized after the 20th week of pregnancy. There are early and late onset types of RLS. The early form begins <45 years of age, is slowly progressive, with 50% reporting an AD familial pattern of inheritance (risk for RLS is up to 6 times greater in first degree relatives), with a major susceptibility locus on chromosome 12q. The late onset may have symptoms that either remain stable after onset, or that rapidly progress over a 5-year period. Etiologic factors may relate to physiologic mechanisms associated with relative central dopamine and iron deficiencies (serum ferritin <18 to 50 μg per liter, iron-saturation <16% to 20%).
2. **Periodic limb movement disorder (PLMD)**. PLMS are reported in 80% to 90% of patients with RLS, in up to 34% of patients >60 years of age, and in up to 15% of insomniacs. When PLMS are significantly elevated and they have an adverse effect on sleep or daytime functioning, the diagnosis of PLMD is made. PLMD can be exacerbated by tricyclic antidepressants, monoamine oxidase inhibitors, and hypnotics, and during withdrawal from benzodiazepines, barbiturates, and anticonvulsants. On PSG, the PLMS appear as elevated, predominantly 50 to 150 Hz, EMG activity from the tibialis anterior muscle, which persists for 0.5 to 5.0 seconds and coincides with episodes of repetitive, stereotypic extensions of the large toe with ankle, knee, and hip flexion.

Consecutive movements have an intermovement interval ≥5 seconds and ≤90 seconds (generally 20 to 40 seconds), and occur primarily in stage N2 sleep. PLMS are considered significant when the PLM index (the average number of PLMS per hour of sleep) is >5 in children, and >15 in adults. New actigraphic monitors with high sampling rates can adequately detect PLMS and promise to be a powerful research tool to study the known night-to-night variability of PLMS.

3. **Rhythmic movement disorder (RMD)**. RMD primarily affects children. The movements are sleep-related, stereotypical, repetitive movements of the head, neck, or large muscle groups and often are associated with rhythmic vocalization that includes head banging, body rocking, and leg banging. Rhythmic body movements often begin in normal children between 8 and 18 months of age and rarely lead to injury. These movements generally resolve by 5 years of age, although persistence may be associated with stress, stimulus deprivation, or CNS lesions. Family members generally are concerned about the noise and sometimes violent nature of these behaviors. PSG studies have shown that rhythmic movements tend to arise from stage N1 or N2 sleep and occur with a frequency of 0.5 to 2 Hz. A series of movements generally lasts <15 minutes.

III. OTHER INVESTIGATIONAL TOOLS AND OPTIONS

A. The maintenance of wakefulness test (MWT). The MWT is a MSLT variant that is performed while the patient attempts to maintain wakefulness in an environment conducive to sleep (a warm, dark room, while lying in a semireclining position). The sleepiness documented utilizing an MWT may more accurately translate to a work situation when compared with the MSLT. The AASM Standards of Practice Committee recommends the MWT begin 2 hours after awakening from overnight sleep. It consists of 4, 40-minute naps; each nap separated from the next by a 2-hour interval. A mean sleep latency <8 minutes is abnormal, whereas values between 8 and 40 minutes are of uncertain value. The use of an MWT has been approved in some occupations where sleepiness is hazardous, to justify a change in employment, and to support disability. No sleep is the strongest evidence for the ability to maintain wakefulness, but does not guarantee safety in regard to hypersomnolence.

B. Brain imaging and electroencephalography. In some hypersomnias due to a medical condition, imaging of the brain and routine EEG may be of prognosticating value. In post-traumatic coma with hypersomnolence, radiographic evidence of hydrocephalus predicts poor treatment response. In AD, clinical progression, secondary to degeneration of cholinergic neurons in the basal forebrain, often correlates with EEG loss of sleep spindles, slow waves, and REM sleep patterns. The use of extended PSG montages, which have extra channels, can allow more thorough assessment of variables such as the EEG (for nocturnal seizures) and EMG (for sleep-related movement and behavior disorders). Daytime provocative studies can be used to appropriately characterize phenomena such as cataplexy.

C. Others. Routine laboratory studies may be needed to rule out anemia, hypoxemia, infection, and metabolic and endocrinologic abnormalities. A Minnesota Multiphasic Personality Inventory with an interview by a neuropsychologist or psychiatrist familiar with sleep disorders can be helpful in cases in which an affective disorder is suspected. There is promise that for a number of intrinsic sleep disorders, such as narcolepsy, genetic testing may help to confirm the diagnosis.

D. Referral to a sleep disorder center. When sleep problems persist, greatly impair quality of life, or necessitate formal sleep studies for diagnosis or therapy (as SRBDs and narcolepsy), referral to a reputable sleep disorder center should be considered.

IV. SUMMARY

The general approach to the patient with a sleep disorder should always begin with the sleep history. The many specific questions necessary for diagnosing a variety of unique sleep disorders are neatly summarized in the ICSDs. The use of PSG is essential in the diagnosing SRBDs, hypersomnias of central origin, and the RBD. The MSLT can delineate the types of pathologic sleepiness specific to narcolepsy and idiopathic hypersomnolence, whereas the MWT has been used assess treatment efficacy and job suitability. In certain cases, basic metabolic panels, drug screens, genetic testing, and a variety of laboratory studies, including ABGs, complete blood counts, and renal function tests are of value. Occasionally, brain imaging, to address potential lesions affecting the ARAS and specific wake/sleep CNS centers is important. An approach that properly combines clinical acumen with the appropriate diagnostic tools generally leads to a solid diagnosis, which allows successful therapeutic interventions.

Recommended Readings

American Academy of Sleep Medicine. *International Classification of Sleep Disorders: Diagnostic and Coding Manual.* 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.

Dyken ME. Cerebrovascular disease and sleep apnea. In: Lenfant C, Bradley TD, Floras JS, eds. *Sleep Apnea: Implications in Cardiovascular and Cerebrovascular Disease*. New York, NY: Marcel Dekker; 2000:285–306.

Dyken ME, Lin-Dyken DC, Poulton S, et al. Prospective polysomnographic analysis of obstructive sleep apnea in Down syndrome. *Arch Pediatr Adolesc Med*. 2003;157:655–660.

Dyken ME, Lin-Dyken DC, Seaba P, et al. Violent sleep related behavior leading to subdural hemorrhage: polysomnographically documented REM sleep behavior disorder with split-screen electroencephalographic-video analysis. *Arch Neurol.* 1995;52:318–321.

Dyken M, Lin-Dyken, Yamada T. Diagnosing rhythmic movement disorder with video-polysomnography. *Pediatr Neurol.* 1997;16:37–41.

Dyken ME, Rodnitzky R. Periodic, aperiodic and rhythmic motor disorders of sleep. *Neurology.* 1992;42:68–74.

Dyken ME, Somers VK, Yamada T, et al. Investigating the relationship between stroke and obstructive sleep apnea. *Stroke*. 1996;27:401–407.

Dyken ME, Yamada T, Glenn CL, et al. Obstructive apnea associated with cerebral hypoxemia and death. Neurology 2004;62:491–493.

Dyken ME, Yamada T, Lin-Dyken DC. Polysomnographic assessment of spells in sleep; nocturnal seizures versus parasomnias. *Semin Neurol.* 2001;21(4):377–390.

Dyken ME, Yamada T, Lin-Dyken DC, et al. Diagnosing narcolepsy through the simultaneous clinical and electrophysiologic analysis of cataplexy. *Arch Neurol.* 1996;53:456–460.

Iber C, Ancoli-Israel S, Chesson A, Quan SF; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.

Kushida CA, Littner MR, Morgenthaler T, et al. Practice Parameters for the Indication for Polysomnography and Related Procedures: An Update for 2005. Sleep 2005;28(4):499–521.

Littner MR, Kushida C, Wise M, et al. Practice Parameters for Clinical Use of Multiple Sleep Latency Test and the Maintenance of Wakefulness Test. Sleep 2005;28(1):113–121.

Practice parameters for clinical use of multiple sleep latency test and the maintenance of wakefulness test. *Sleep.* 28(1):113–121.

Arand D, Bonnet M, Hurwitz T, et al. The clinical use of the MSLT and MWT. Sleep 2005;28(1):123–144.

Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep.* 1999;22(5):667–689.

Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328:1230–1235.

Young T, Peppard P, Palta M, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med.* 1997;157:1746–1752.

CHAPTER

10 Approach to the Patient with Visual Loss

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Visual loss as a primary complaint varies depending on whether one or both eyes are affected. Is the visual loss abrupt in onset, gradual or is it suddenly discovered long after onset? Is the visual loss complete or partial? Finally, does the visual loss include visual hallucinations or illusions? The causes of visual loss rapidly narrow down to a very small number of possibilities based on the temporal sequence of the patient's symptoms, age, and sex, and the presumed anatomic location of the lesion (Table 10.1).

Patient's visual complaints usually first seek an ophthalmologist or optometrist. Referral to a neurologist from the ophthalmologist usually includes a CT or MRI already in hand. If the problem appears to be a tumor, the eye specialist will most often refer the patient directly to a neurosurgeon.

The visual pathway provides a number of diagnostic constellations of easily examined elements that can be carried out at the bedside. The pupils, the retina, and the optic disc can be objectively examined. Subjective visual tests include color, visual acuity, and visual fields, and these help to direct localization to the retina optic nerve, chiasm, optic tract, lateral geniculate, geniculocalcarine tract, and visual cortex. Damage to visual association cortices, especially parietal and inferior temporal, will produce higher function disturbances such as central achromatopsia, alexia without agraphia, prosopagnosia, and Anton's syndromes.

I. BEDSIDE OR OFFICE CLINICAL EXAMINATION OF THE VISUAL SYSTEM

A. Visual acuity (high contrast/low contrast). Although it is best to examine visual acuity using a distance Snellen chart, the neurologist almost always examines visual acuity using a handheld Rosenbaum card or a Jaeger print card. If a near card is used, be sure that the patient has their glasses on. In the office you can keep a pair of drugstore reading glasses of plus 2 or plus 3 for those patients over 40 years old who have forgotten their reading glasses. Push the patient to give you the very best acuity possible. Do not take no for an answer. Do not rush them. Start by telling them the first letter or number of the line and allow them to move the card back and forth. Do not begin with the largest letter; rather, ask the patient to read the 20/30 and the 20/25 lines and finally the 20/20 lines. If that fails, gradually work your way down the card. If the patient cannot read any letters on the Snellen card, the next approach is counting fingers. Three fingers held up are the equivalent of the big E on the distance acuity chart. A patient who can count fingers at 20 feet has 20/200 acuity. Thus counting fingers at 5 feet would be a rough equivalent of 20/800. If they cannot count fingers, try hand movements. If the patient cannot detect hand movement, try light perception by turning a hand light off and on. If the patient sees light reliably, see if the light can be localized in space, above, below, or side to side.

Visual acuity should be normal with a retrochiasmal pure HH or with a pure bitemporal hemianopia. Acquired visual acuity deficits not due to refractive error (nearsightedness or farsightedness) imply that macular or central vision is defective. Loss of Snellen acuity is commonly accompanied by other central visual loss such as defective color vision, Amsler's grid defects, pallor of the optic disc, evidence of macular disease and, if unilateral, a RAPD. Bilateral, but grossly asymmetrical, retinal or optic nerve visual loss will also show an RAPD in the eye with the greatest field loss.

B. Confrontation visual fields should be performed at a distance of 1 m from the patient. Have the patient cover one eye with the palm of the hand and direct him to look at

TABLE 10.1 Sources of TMVL

- Intraocular
  - Recurrent hyphema
  - Glaucoma[a]
  - Papilledema[a]
  - Disc drusen[a]
  - Congenital cavitary disc anomalies[a]
  - AION
    - Arteritic (due to giant cell arteritis)
    - Non-arteritic rarely causes TMVL
    - Choroidal insufficiency (ocular ischemia syndrome)
- Intraorbital (intermittent vascular compression)
  - Hemangioma
  - Osteoma
  - Meningioma
- Intracranial
  - AVMs
  - Brain tumors
- Embolic to retina (central or branch retinal artery occlusion)
  - Intracranial aneurysm
  - Cardiac
  - Valvular debris
    - Infective endocarditis
    - Rheumatic valvular disease
    - Bicuspid aortic valve
    - Mitral valve prolapse
  - Clot
    - Congenital cardiac malformations
    - Atrial fibrillation
    - Ventricular subendocardial ischemia
    - Akinetic segment
    - Ventricular aneurysm
    - Right-to-left shunt
    - PFO Patent Foramen Ovale
    - ASD Atrial Septal Defect
    - ASA Atrial Septal Aneurysm
    - Atrial myxoma
- Aortic atherosclerosis
- Carotid disease
  - Dissection
  - Atherosclerosis
  - Fibromuscular dysplasia
- Fat embolism
  - Pancreatitis
  - Long bone and flat bone fractures
- Hematologic
  - Polycythemia
  - Sickle cell disease
  - Thrombocytosis
- Hypotension[a]
- Demyelinating disease
  - Uhthoff's phenomenon
- Vasospasm
  - Hypertensive crises especially high in paraplegic or quadriplegic patients
- Migraine

[a]These causes of TMVL usually last seconds and are known as transient visual obscurations or TVO. They are frequently binocular as well as monocular.

your nose. Divide the visual field in front of the patient into an imaginary plane of superior and inferior nasal and temporal quadrants. The center of the visual field is your nose. Present your fingers (one, two, or five) rapidly in the periphery of each quadrant. Redirect the patient's attention to your nose and not to look at your fingers. Slowness or failure to respond accurately in one quadrant or hemifield may be the earliest sign of a homonymous field loss. After rapid finger counting, present your hands, palms forward, first in the two upper quadrants, then in the lower quadrants. Ask the patient to compare the palms for brightness and clarity. Finally, place the index finger of one hand on your nose and the index finger of the other hand on the peripheral nasal, temporal, superior, and inferior fields. Have the patient look at your nose and ask which finger is brightest and clearest. This tests for a central scotoma. You can also place one hand above and one below the horizontal meridian and have the patient look at your nose. This allows the patient to compare hands for brightness and clarity and helps identify altitudinal visual field defects as are seen with retinal and optic disc diseases, especially anterior ischemic optic neuropathy (AION) or BRAO.

C. Color vision testing. A book of Ishihara or Hardy–Rand–Rittler pseudoisochromatic color plates can be used to test color vision one eye at a time. Although these tests were designed to identify red-green color blindness, they can be used as a rough indicator of color acuity, which is another test of central macular function. Test one eye at a time when looking for evidence of unilateral optic nerve damage. About 1% or 2% of men are red-green color blind or defective as are 0.5% of women. There are other, more complicated, color tests but neurologically they provide no more information.

D. Pupil tests. The single most important and useful objective bedside test of anterior visual pathway function is the pupillary light response. When the ganglion cells or their axons in one eye, optic disc or optic nerve, are damaged, the pupil reaction to light will be less vigorous in the affected eye as compared with the unaffected or normal eye. If both optic nerves or retinas are damaged, a relative afferent pupil defect will be seen in the eye with the largest amount of visual field loss. ***There is no such entity as a bilateral relative afferent pupil defect.*** The RAPD is a defect in the reaction to light of one eye ***relative*** to the other. One should swing the light from eye to eye allowing it to rest for 1-second intervals and there will be a brisker reaction (a more complete response) to light in the normal unaffected eye and a less brisk reaction or dilation of the pupil in the affected eye. This is the *RAPD*. If one eye is blind, the direct reaction to light will be absent—this is an *amaurotic pupil*. For details of the RAPD, refer to Chapter 12.

E. Ophthalmoscopy. Ophthalmoscopy is an objective part of the neuro-ophthalmologic examination. Recognition of changes in the optic disc is a key to the diagnosis of diseases affecting the anterior visual pathways. Details of this part of the examination are not considered in this chapter. When in doubt, dilate the pupils (with two drops of 2.5% epinephrine or 1% mydracil eye drops) for a good look. Observe and record the size of the ratio of cup to disc, appearance of the vessels, whether there are hemorrhages, exudates, or pigment changes or swelling of the disc.

F. Visual evoked potentials (VEPs). This test tends to be overused by neurologists in the evaluation of the visual pathways, but it can be especially valuable in the patient with a past history suggestive of optic neuritis (ON) where visual acuity is normal, there is no color vision loss and only slight optic disc pallor. Such patients frequently have a prolonged P100 latency. The VEP can be useful in patients suspected of functional visual loss. Patients, however, can confound the VEP by focusing in the distance, past the VEP screen, and thereby alter p100. A normal VEP latency in this setting is useful, but an abnormal latency may be a red herring.

G. Electroretinography (ERG) is a test of retinal receptor function most commonly used to detect conditions like retinitis pigmentosa and paraneoplastic retinopathies. With certain bilateral retinopathies this may be a definitive test.

H. Formal visual field testing consists of three types of tests.

Tangent screen exam is rarely used today. It is carried out on a flat black felt screen located 1 m away from the patient. It can be especially helpful in that it allows the examiner to back the patient up to 2 or 3 m and can be used to look for functional "tunnel" vision or to magnify small central visual defects.

Kinetic perimetry is carried out on a Goldmann perimeter using variable size and brightness lights and uses a supra-threshold kinetic technique. It is done in an ophthalmologist's office. This form of perimetry is technician-dependent and has largely been supplanted by static perimetry.

Static perimetry done on Humphrey® or Octopus perimetry® tests threshold static targets presented at every 2° and tests the inner 24° to 30° of the visual field. This test is also done in an ophthalmologist's office and is the usual formal perimetry done today.

II. ACUTE TRANSIENT MONOCULAR VISUAL LOSS

A. Clinical features. Acute transient monocular visual loss (TMVL), also called amaurosis fugax, is relatively common and has a host of different causes (Table 10.1). Before concluding that the patient has had a monocular event, explore the possibility that the "monocular" event was really a transient binocular HH. This is particularly true if the visual loss is followed by a headache. Patients with homonymous visual defects rarely complain that half of objects are gone or that they cannot see well to one side. The patient may insist that they closed one eye or the other and the visual loss was only unilateral, but this is just seeing what they think they should be seeing. Monocular visual loss is occasionally reported as being sudden in onset when in reality it is ***suddenly discovered*** when the unaffected normal eye was covered and the patient suddenly appreciates that they could not see well out of the affected eye. It is understandable why the patient would assume

visual loss was sudden. The mystery is why some people do not detect severe visual loss in one eye until it is brought to their attention. A most common cause of true transient monocular visual loss is artery-to-artery or cardiac-to-artery embolism, but there are many other causes of transient or permanent acute visual loss (Fig. 10.1).

B. Approach to transient monocular visual loss.

1. Be sure that the spells occur in one eye and are not homonymous.
2. Look for ophthalmoscopic evidence of asymmetric optic disc cupping (glaucoma), optic disc anomaly, optic disc swelling, or residues of retinal embolism (hemorrhages, exudates, embolic plugs of cholesterol, platelets, fibrin, or calcium).
3. Look for a relative afferent pupil defect, visual field loss in both eyes, loss of visual acuity, and finally whether color vision is equal and normal in both eyes.
4. Look for proptosis (sign of intraorbital disease) causing intermittent amaurosis due to vascular compression particularly occurring with eye movement.
5. Auscultate the heart and carotid arteries for murmurs and bruits.
6. Laboratory studies.
   a. CBC, including platelet count.
   b. Sedimentation rate (ESR)—In all patients over age 50.
   c. C-reactive protein (CRP)—In all patients over age 50.

   In patients of age 40 or less, strongly consider evaluation for hypercoagulable states:
   a. Protein C.
   b. Protein S.
   c. Factor V Leiden.
   d. Antithrombin.

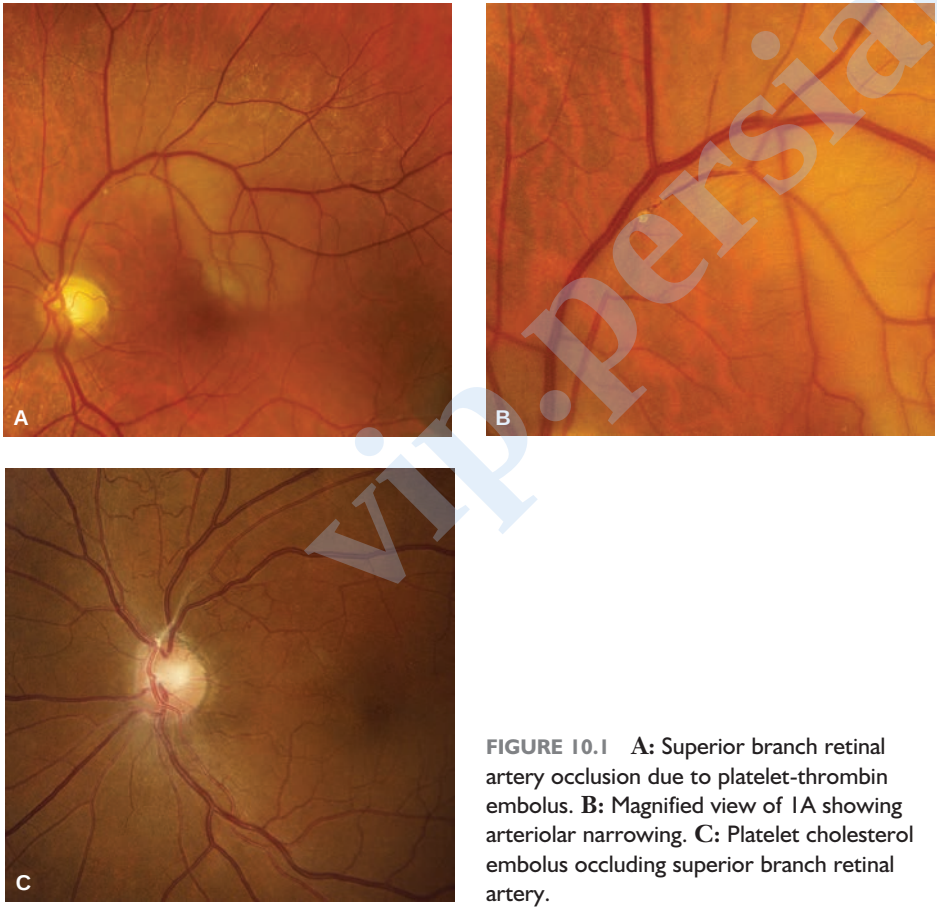


FIGURE 10.1 **A:** Superior branch retinal artery occlusion due to platelet-thrombin embolus. **B:** Magnified view of 1A showing arteriolar narrowing. **C:** Platelet cholesterol embolus occluding superior branch retinal artery.

e. Prothrombin gene mutation 20210A.
f. PT (INR) and aPTT.
g. Lupus anticoagulant (LA).
h. Anticardiolipin antibodies (IgG, IgM, and IgA).
i. Fibrinogen.

7. Transesophageal echocardiogram, looking especially at the aortic arch, the interatrial septum and left atrial appendage for evidence of patent foramen ovale (PFO), atrial septal defect (ASD) and/or atrial septal aneurysm (ASA), or transthoracic echocardiogram with agitated saline bubble study.
8. Perform carotid Doppler ultrasound and transcranial Doppler.
9. Consider an MRA, Computed tomography angiography (CTA), or four vessel catheter angiography.

Carotid artery emboli are not the only cause of TMVL, and there may be more than one convincing potential cause of TMVL in a single patient. It is always valuable to refer the patient with TMVL for examination by an ophthalmologist who can measure intraocular pressure, perform a dilated indirect ophthalmoscopic examination, perform formal visual fields, and obtain fundus photos. Most patients with TMVL seen by neurologists have already been seen by an ophthalmologist or optometrist if the primary complaint is visual. Be sure that the ophthalmic examination recommended above is performed.

III. SUBACUTE MONOCULAR VISUAL LOSS

Subacute monocular visual loss may occur in 2 age groups: 15 to 45 years of age where it is usually painful especially with eye movement and in those over the age of 50 years where it is commonly stepwise and usually painless.

A. Clinical syndromes.

1. **Optic neuritis.** This condition occurs in younger patients and presents with painful (>90%) monocular visual loss. Pain may precede the onset of visual loss by a few days and is worse with eye movement. Visual loss is characterized as a "skim, scum, blur, fog, or haze" or may be described as if there were a cloud in front of the eye. Vision may also be characterized as dim, dark, or bright. Colors are dim, washed out or gone entirely, and low-contrast images will be lost. One-third of patients with ON will have a swollen optic disc (optic papillitis). Occasionally, patients complain of photopsias (spots and sparkles) occurring with loud noise. Visual acuity may range from 20/20 to no light perception, but 20/50 to 20/200 is the rule. The visual field loss is typically monocular and is central and/or altitudinal. Prognosis for return of visual acuity to 20/40 or better is the rule and occurs within weeks. If visual acuity remains severely depressed, obtain a neuromyelitis optica (NMO) antibody.
2. **AION.** The older patient with monocular painless, acute, occasionally stepwise visual loss, most commonly appreciated on awakening in the morning, is suffering from hypotensive ischemia of the optic disc known as **AION.** This condition has two forms.
   a. **Non-arteritic AION (NAION).** The non-arteritic form is related to hypotensive ischemia predisposed to by an anatomically small cupless optic disc through which all 800,000 to 1,200,000 axons of the optic nerve pass, on their way to the chiasm and beyond. This small, tightly packed "disc at risk" is a setup for an ischemic cascade that may occur either abruptly or in a stepwise fashion over a few days (Fig. 10.2). The NAION is usually painless and characteristically produces inferior altitudinal, inferior nasal quadrantic, and/or central scotomatous visual field defects. Twenty-five percent of patients with NAION in one eye will have the second eye affected within 2 years.
   b. **Arteritic AION (AAION).** The obvious major difference between NAION and the arteritic form of AION is age. AAION is caused by giant cell arteritis (GCA), a disease occurring in the elderly. GCA should be considered when symptoms include a new kind of headache, usually continuous, with soreness of the scalp, and occasional brief amaurotic attacks due to recurrent choroidal ischemia. Symptoms of polymyalgia rheumatica (PMR) include tenderness of the scalp, jaw claudication, aching pains

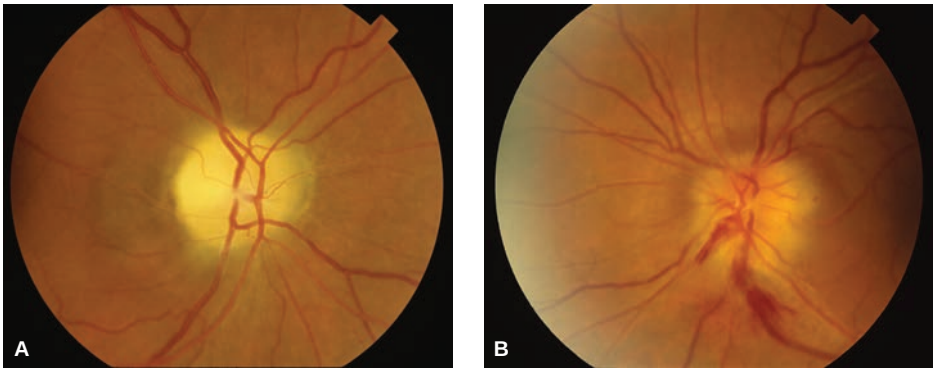


FIGURE 10.2 Old and new NAION in the same patient. **A:** The right disc affected 1 year ago shows ischemic altitudinal pallor. **B:** The left disc is acutely swollen with splinter hemorrhages which occurred the day before the photo was taken.

in the shoulders and hips, anorexia, weight loss, fever, and night sweats. The occult form of AAION in which there are no PMR symptoms occurs 20% of the time. AAION causes sudden severe, devastating permanent visual loss. It is a diagnostic and therapeutic emergency. Visual acuity is usually 20/200 or less and the visual field shows an altitudinal defect with a large central scotoma or complete blindness. There is an RAPD. With total blindness in one eye there is an amaurotic pupil. In addition to an ESR, CRP, and CBC, a temporal artery biopsy should be performed. As with NAION, the disc is swollen, but it is usually very pallid with a few small splinter hemorrhages. (Fig. 10.3) Prognosis for visual return is poor. Risk of second eye involvement, if giant cell arteritis (GCA) is left untreated, is very high. Treatment is immediate high dose corticosteroids, given as soon as the diagnosis is suspected.

c. **Leber optic neuropathy.** Leber optic neuropathy is an inherited disorder of mitochondrial DNA. It presents as subacute, painless, monocular visual loss over days characteristically seen in men in the teens to twenties (8:1 men to women). The second eye becomes similarly affected weeks to months after the first eye (Fig. 10.4).

The disc appears slightly swollen with tortuous small telangiectatic vessels on the disc surface. After a few weeks, the nerve fiber layer becomes atrophic, particularly in a temporal wedge of the papillomacular bundles. This nerve fiber loss is most prominent between the 7 and 11 o'clock hours in the right eye and the 1 and 5 o'clock hours in the left eye. Later, as more nerve fibers are lost, both discs become diffusely pale. Visual acuity loss ranges from 20/80 to 20/800, and there are dense central scotomas that may break out into the periphery. Confirmation of the diagnosis is made with the identification of mitochondrial DNA for appropriate mutations.

B. Approach to subacute monocular visual loss.

1. Historically determine the pace of visual loss. Was it actually suddenly discovered, or was there gradual and progressive visual dysfunction in the eye, or was the visual loss abrupt and remained poor?
2. Look for evidence of earlier optic disc swelling or pallor and for evidence of embolic material in the arterioles. Look also for pigment changes characteristic of infections, inflammation, or "bone spicule" clumps seen in retinitis pigmentosa. Dilate the pupils.
3. Look for a relative afferent pupil defect, do confrontation visual fields, document visual acuity, and record color vision one eye at a time. Obtain fundus photographs and formal visual fields.
4. Decide whether visual loss appears to have been due to embolic vascular disease in which case you will proceed as if there was an embolic source.
5. If the visual loss appears to be due to ON (pain on eye movement and subacute progressive visual loss over a few days), proceed to MRI and lumbar puncture to look for evidence of demyelination.

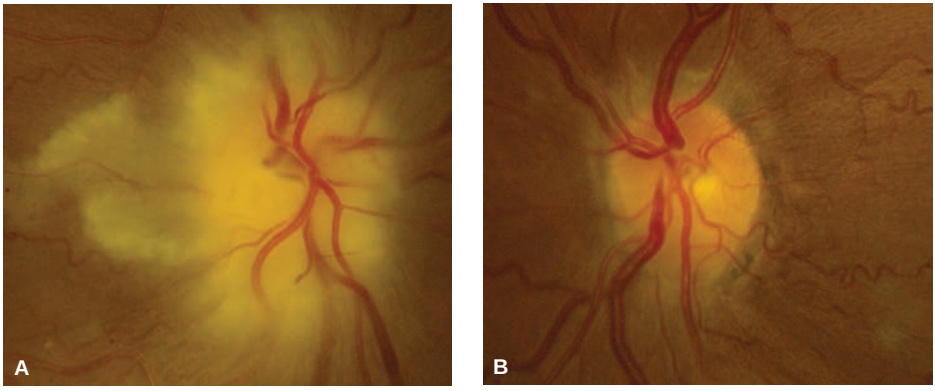


FIGURE 10.3 Pallid complete disc swelling that includes cilio-retinal arteriolar occlusion in **A** and normal in **B**.

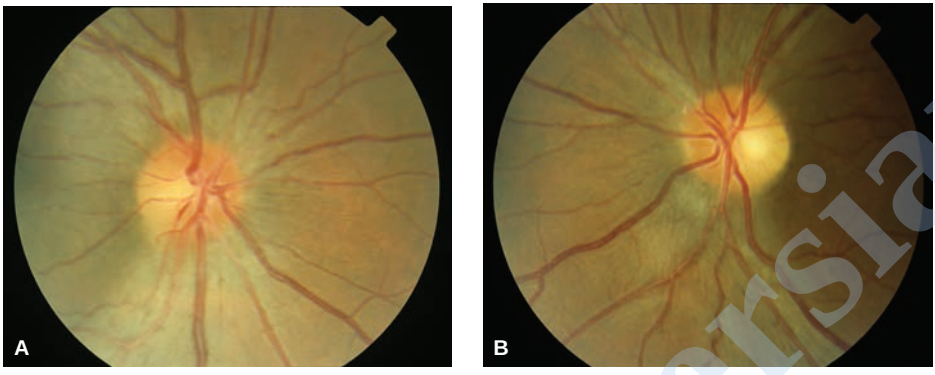


FIGURE 10.4 Leber optic neuropathy. Right eye is acutely affected and the left eye was previously affected with large segment of temporal nerve fiber layer dropout and temporal pallor of the disc.

6. If it appears that the visual loss was actually gradual in onset or has been present longer than recognized and there is evidence of optic disc pallor, do an MRI to look for a compressive lesion from the globe to orbital apex to optic chiasm.

IV. THE SYNDROME OF CHRONIC PROGRESSIVE MONOCULAR VISUAL LOSS

The syndrome of chronic progressive monocular visual loss is a characteristic of optic nerve compression. Visual acuity may well be normal early, but the patient will notice that something is not quite right. They complain of a blur or a smudge and may repeatedly clean their glasses or have their refraction checked and rechecked resulting in one of the "handful of glasses" syndromes (Table 10.2). Compressive visual loss is usually painless. If the optic nerve is compressed by a mass within the orbit, there may be proptosis, limitation of ocular motility, eye movement-induced transient, conjunctival congestion, and chemosis. If optic nerve compression occurs within the optic canal or intracranially, proptosis will occur late or may not occur at all.

Severe loss of visual acuity may occur rapidly, and visual field testing reveals a central scotoma that may break out into the periphery. Color vision will be defective in the affected eye,

TABLE 10.2 "Handful of Glasses" Syndromes

Early optic nerve compression
Bitemporal hemianopia with hemifield slide
Alexia without agraphia
Bilateral small occipital tip infarcts
Vertical eye movement-induced myopia with convergence-retraction nystagmus—the dorsal midbrain syndrome

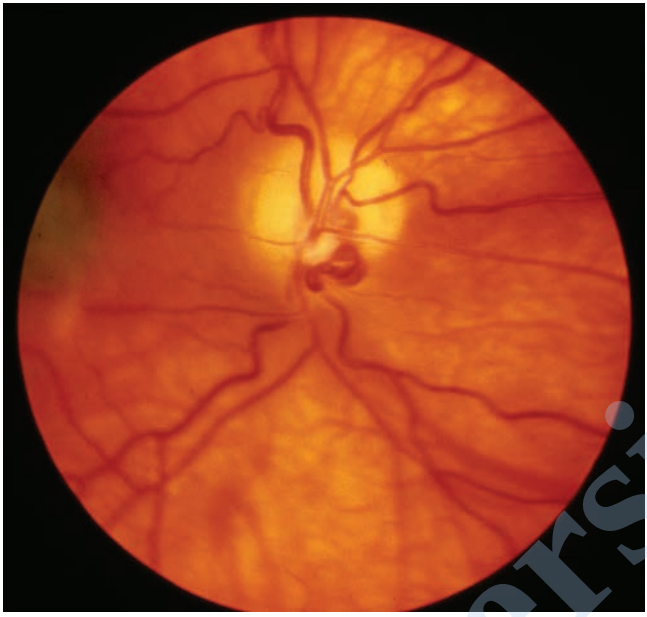


FIGURE 10.5 Swollen pallid disc with retino-choroidal collateral veins caused by an optic nerve sheath meningioma.

and there is an RAPD in the affected eye. Optic disc swelling, or disc pallor, or a combination of pallid swelling is common. Retino-choroidal collateral vessels may develop on the disc. These vessels are evidence of chronic disc swelling and retarded venous drainage. They may also be seen in end-stage glaucoma but most commonly they are the result of retrobulbar strangulation of the optic nerve by meningioma, glioma, sarcoidosis, or disc swelling of any cause (Fig. 10.5).

The VEP in the early stages of optic nerve compression when visual acuity is normal or near normal will show a prolonged P100. After visual acuity has dropped, VEP latency becomes strikingly prolonged and the VEP amplitude flattens. Consultation with an ophthalmologist is appropriate and should be done to rule out other potentially treatable ocular causes of visual loss. Ask for formal visual fields, photos of the optic discs, and intraocular pressure measurement.

V. BINOCULAR VISUAL LOSS THAT IS ABRUPT IN ONSET

Binocular visual loss that is abrupt in onset (Table 10.3) is occasionally due to bilateral optic disc disease such as ischemic optic neuropathy or ON, especially Devic disease or NMO. When this scenario occurs, the patient typically announces that the vision in both eyes has acutely or subacutely been lost. On examination, most commonly, one optic disc is pale and atrophic, evidence of earlier damage, and the other disc is swollen by new damage. This ***"Foster Kennedy syndrome"*** is attributed in most textbooks to a frontal tumor

TABLE 10.3 Causes of Bilateral Visual Loss—Anterior Visual Pathways

Ocular causes
Anomalous discs
Papilledema—of any cause
Disc drusen
Pseudo-Foster Kennedy syndrome (bilateral AION)
Toxic—nutritional (tobacco–alcohol amblyopia), B_{12} deficiency
Medications—ethambutol, chloramphenicol, Plaquenil, thioridazine
Leber optic neuropathy
Neuromyelitis Optica NMO (Devic disease)
Sarcoidosis
Intracranial causes
Chiasmal
Tumor (craniopharyngioma, Rathke's cleft cyst, pituitary tumor, meningioma and other rarer tumors)
Pituitary apoplexy
Aneurysm (ophthalmic or anterior cerebral)
Sphenoid mucocele
Trauma (chiasmal tear)
Demyelination
Toxic/metabolic
Vascular (dolichoectatic anterior cerebral artery)
Combined chiasmal and optic nerve disease due to any of the above will give combinations of bitemporal and central visual loss
Optic tract
Tumor—same as chiasm
Demyelination
Trauma
Stroke

causing ipsilateral compressive visual loss and optic atrophy combined with papilledema due to increased intracranial pressure in the contralateral eye. The most common cause of this ophthalmoscopic combination of atrophy in one eye and disc swelling in the other is a "**pseudo-Foster Kennedy syndrome,**" caused by bilateral, *sequential* AION in a patient who did not notice visual loss in the first eye to be affected (the eye with disc pallor). (Fig. 10.2). The subsequent loss of vision with disc swelling in the previously unaffected eye suddenly plunges the patient into unexpected bilateral visual loss.

Transient visual obscurations (TVO) occur in patients who have papilledema, drusen of the optic disc, and other disc-related conditions (see Table 10.1). These TVOs are seconds-long transient bouts of unilateral or binocular visual dimming or blindness frequently precipitated by Valsalva maneuvers or postural change. Examination of the fundus photos and B-mode scans should identify the congenitally anomalous swollen discs.

Binocular visual loss, which is abrupt in onset, occurs rarely following arteriographic procedures. Posterior fossa angiography and coronary angiography will also, occasionally be attended by what appears to be a toxic reaction to iodinated contrast associated with vasospasm. Permanent visual loss owing to such toxic contrast responses is rare.

VI. BINOCULAR VISUAL LOSS DUE TO CHIASMAL DAMAGE

Binocular visual loss due to chiasmal damage is seen in the pure form where there is no concomittant damage to optic nerves or optic tracts.

A. Clinical features.

1. **Bitemporal visual loss**. If the lesion causing bitemporal visual loss arises from below (typically a pituitary adenoma), visual loss is dense in the superior bitemporal visual field. If the lesion originates from above (typically an aneurysm of the anterior cerebral

artery or craniopharyngioma), the visual field defect will be in the inferior bitemporal visual fields. Complete, macula-splitting, bitemporal defects are usually due to tumor or traumatic chiasmal tears.

The patient with bitemporal visual loss rarely complains of loss of peripheral vision, but their symptoms are caused by instability of the two preserved nasal visual fields that abut the midline. The visual complaints consist of intermittent and brief doubling of objects, loss of objects, and strange visual effects that occur as a result of vertical sliding of the one hemifield relative to the other. This "slip" in the retinas causes the right half of images to slip vertically and/or horizontally in relation to the left half. This odd group of symptoms is collectively known as the "**hemifield slide phenomena**" and is another cause of the "handful of glasses" syndrome (Table 10.2). As patients with visual symptoms see eye doctors first and are rarely able to articulate the nature of the visual dysfunction, they are commonly provided with a new refraction, particularly if confrontation or formal visual fields are not performed.

2. **Junctional syndrome.** If the chiasmal compression occurs where the optic nerve enters the chiasm, symptomatic optic nerve compression occurs in that eye (see IV) and asymptomatic superior temporal quadrantic visual loss is found in the contralateral eye. This is caused by damage to fibers from the inferior nasal part of the contralateral eye and the optic nerve at its junction with the chiasm. This visual field combination of central scotoma in one eye and a superior temporal defect in the other eye is known as a **junctional syndrome.**
3. **Pituitary apoplexy.** Abrupt onset of unilateral or bilateral visual loss usually combined with ocular motility disturbances due to paralysis of cranial nerves III, IV, and VI, associated with headache, agitation, fever, stiff neck, and occasionally blood in the CSF, occurs with acute hemorrhage into a pituitary tumor or the pituitary gland. This may occur spontaneously or result from embolic infarction following carotid endarterectomy or cardiac surgery. The diagnosis is confirmed with an MRI or CT scan. Patient agitation frequently makes these studies less than optimal for interpretation. Pituitary apoplexy only occasionally causes pure visual loss; there is usually some ocular motility disturbance. The diagnosis of pituitary apoplexy should rank high on the list of causes of sudden onset of bilateral visual loss.
4. **Combination of central and bitemporal visual loss.** Both optic nerves may be gradually compressed with large lesions that also compress the chiasm. This may cause unilateral and bilateral central visual loss and a roughly bitemporal visual field defect. Unless the bitemporal field loss is complete, it is rare for the area of field loss to be equal in both eyes. Thus the eye with the greatest visual field loss will have an RAPD.

B. Clinical approach to binocular visual loss that is subacute or chronic.

1. Historically look for symptoms consistent with hemifield slide. Ask which eye seems to be affected most severely.
2. Do confrontation visual fields to look for bitemporal and/or central visual field loss. Do visual acuity and color vision testing to look for evidence of optic nerve dysfunction. Perform ophthalmoscopy to look for evidence of optic disc swelling, pallor, or retinal hemorrhages.
3. A CT or MRI should be done to look at the suprasellar space, the pituitary fossa, and sphenoid sinus and cavernous sinuses.
4. Fundus findings in chiasmal compression depend on the nature of the lesion and if there is increased intracranial pressure. Papilledema is rarely seen with pituitary adenomas unless the tumor causes hydrocephalus. Optic atrophy with nerve fiber loss may preclude the development of disc swelling. For reasons that are not clear, disc swelling is fairly common with craniopharyngiomas as is severe optic atrophy.

VII. BILATERAL VISUAL LOSS DUE TO HOMONYMOUS HEMIANOPSIA

Bilateral visual loss due to HH can be due to lesions in the optic tract, the lateral geniculate nucleus, geniculocalcarine tract, or occipital cortex. Total bilateral right and left homonymous visual loss is very rare.

A. Localization of lesions. If a hemianopia is complete and splits fixation and there are no other symptoms or signs, the lesion is either in the optic tract, geniculocalcarine tract, or the occipital cortex. Lesions occurring between the lateral geniculate, the geniculocalcarine tract, and visual cortex are rarely complete without creating other neurologic problems such as hemiparesis, hemisensory loss, aphasia, or parietal neglect. Most HH are incomplete, and their location, density, and congruity (super-imposability of one eye's visual field on the other) broadly help to tell where the lesion is located. For practical purposes, CT and MRI provide images of lesions and their location is now rarely a mystery. Homonymous visual field defects owing to tumor, stroke, and arteriovenous malformations (AVM) are easily accounted for with these techniques. Occipital lobe damage will produce pure visual loss if damage is confined to the calcarine cortex. Total loss of calcarine cortex on one side will give a complete HH. Commonly, the macular region of calcarine cortex is "spared" to some extent because a large part of the visual cortex subserves the inner 20° of the visual field. Conversely, small cortical infarcts that occur in the inner 20° of the visual field may cause very small but visually troubling visual field defects that may not be identified by standard perimetry. These visual field defects are best identified using a "magnifying technique" with a tangent screen exam done at 2 or 3 m. These patients complain bitterly of difficult-to-describe loss of vision which cannot be corrected with glasses (Table 10.2) and they go from one eye doctor to another without having the occipital lobe damage discovered.

B. Migraine auras. The most common cause of episodic homonymous visual loss is the visual aura of migraine. These homonymous auras are frequently mistaken by the patient for visual loss in one eye. The characteristic features of this visual event are movement, brightness, and "buildup" of the visual loss usually beginning in the center or off to one side of the center of the visual field. It then moves over minutes toward the periphery of the visual field. The typical auras consist of zigzag lines that are silvery or red, yellow, blue, bright white, and black; they pulsate, turn, swirl, or glimmer. Although most patients characterize this as a "c-shaped" or "horseshoe" shape to one side, occasional patients describe a visual image that is central in both eyes "as if a flashbulb just went off" or an arc of shimmering flashing zigzags in both the right and left fields "like a rainbow." The next most common description is a "heat wave" sensation or the image is of water running down a window. These visual events usually last from 5 to 60 minutes and are followed by a headache. The headache is usually unilateral but may be generalized and need not be particularly severe or long lasting. Some patients have only the visual aura and no headache, so-called *acephalgic migraine*. This is a common event in older migraineurs.

C. Visual seizures occipital lobe epilepsy. Metastatic brain tumors, meningiomas, gliomas, and AVMs may have primary visual seizures with no secondary generalization. These seizures produce homonymous sparkles, flashes, and colors, but, as contrasted with migraine, there is no characteristic "buildup" and progression of the visual event from center to periphery. A CT and MRI will identify these conditions, and EEG will show epileptiform activity.

D. Degenerative diseases. The common causes of HH are benign and leave no trace (migraine) or produce lesions in the brain that can be identified with CT or MRI (stroke or tumor). Creutzfeldt–Jakob disease (CJD) may present with HH (the so-called Heidenhain variety) and rarely patients with Alzheimer disease (AD) may develop HH. The CJD has characteristic MRI and EEG changes, but AD will show no disease specific imaging findings. Progressive multifocal leukoencephalopathy, common in immune-compromised patients, often presents with dense HH and demyelinating changes on MRI, typically sparing the U-fibers.

VIII. SYNDROMES OF VISUAL DISTURBANCE DUE TO HIGHER COGNITIVE DYSFUNCTION

These syndromes can be caused by tumors primary or metastatic, however, most are caused by embolic stroke and are particularly common after cardiac surgical procedures. They frequently go unrecognized and present to the physician with unusual visual complaints.

A. Alexia without agraphia. This syndrome is caused by damage to connections between both visual cortices and the angular gyrus. This is due to either (1) a lesion in the splenial outflow from the right occipital lobe and the connections of the left occipital lobe to the angular gyrus where there is no hemianopia or (2) a combination of a left occipital infarct with a right HH and a callosal splenium lesion. These patients may present to the neurologist with a history of going to many eye doctors for new glasses because they are unable to read (Table 10.2). The diagnosis is particularly problematic when there is no HH.

B. Balint's syndrome. Bilateral damage to the watershed region between the middle and posterior cerebral artery circulation high in the parietal lobes will cause **Balint syndrome,** which consists of visual disorientation, spasm of fixation (apraxia of gaze), optic ataxia (defect in visually guided hand movements), and simultanagnosia (loss of panoramic vision). Although these patients do not deny their visual troubles, they usually suffer in silence because they are frequently unable to adequately verbalize what is wrong. They are not agitated and are not aphasic or demented. Frequently they have alexia without agraphia as well.

C. Bilateral inferior temporal lobe syndrome. Damage to the inferior temporal lobe bilaterally in the region of area V4 of the fusiform gyrus will cause one or both of the following syndromes: **prosopagnosia** (the inability to recognize faces) and **central achromatopsia** (central color vision loss).

1. **Prosopagnosia**. Patients with prosopagnosia present with either bilateral sudden visual disturbance or a previously damaged inferior temporal lobe (which may or may not have been recognized) and then a second lesion in the other inferior temporal lobe. Occasionally, these patients will have only a unilateral lesion, usually of the right inferior temporal lobe. Prosopagnosic patients complain of being unable to recognize individual faces, but they also have trouble picking out their own car from other cars, their dog from other dogs, and so on. In short, while they can identify classes of objects, they have trouble singling out a specific individual within a general class or group without other clues.

   These patients become expert at recognizing features of a person's voice or the way a person walks to garner clues in identifying people. They commonly complain that colors are washed out and that whites (linens, snow) look dirty or brownish. They may have homonymous superior quadrantic visual field defects or may have no visual field loss at all.
2. **Central achromatopsia**. Patients with central achromatopsia involving the entire visual field may also have prosopagnosia or they may have only a hemifield defect in color vision known as hemiachromatopsia. Color loss may be profound or it may consist simply of desaturation and "dirtying" of color complained of by the patients with prosopagnosia. The lesions are inferior temporal in location.

D. Anton syndrome. Extensive bilateral damage to both the occipital and parietal lobes produces visual loss and the denial of blindness known as **Anton syndrome**. These patients confabulate elaborately in response to questions about their visual environment.

E. Approach to patients with homonymous visual field defects.

1. Obtain best corrected visual acuity (even alexic patients can usually read numbers or individual letters).
2. Confrontation visual fields will tell you the completeness and the rough location of the visual field defect.
3. Fundus examination will confirm that there is no significant disease of the retina or disc responsible for the visual loss.
4. A CT scan or preferably an MRI should confirm localization of the lesion(s).
5. Referral should be made to an ophthalmologist for visual fields. Patients who are hemiplegic, aphasic, or have right parietal lesions will not perform fields well, if at all.
6. Neuropsychologic evaluation of patients with higher cortical defects will be helpful.

IX. FUNCTIONAL VISUAL LOSS

The patient with functional visual loss either claims total or partial loss in one eye or both eyes. Whatever the motivation or underlying issue, it is possible to uncover functional *monocular* visual loss simply by looking for an RAPD. In the absence of an RAPD, severe, or even

moderate, significant monocular visual loss does not exist. Patients with functional *binocular* blindness can be uncovered in one of two ways. Use of an optokinetic target (tape or drum) is usually sufficient; however, some patients are able to "look through" these targets. A foolproof method that can be used to uncover a single "blind" eye or bilateral "blindness" is a mirror held in front of the patient's face and then tilted up and down and side to side. This maneuver produces an irresistible sensation of environmental movement and the patient's eyes will involuntarily move to orient the patient in space. Eye movement proves that the patient can see at least partially if the claim has been that of total blindness.

The most difficult problem is that of the patient who presents with moderate functional visual loss that is equal in both eyes (e.g., 20/50 OU). An RAPD is of no help because the visual loss is bilateral and the acuity is too good to make the mirror or optokinetic tangent useful. Remember that it is possible for patients to voluntarily alter the VEP latency and wave form, thus an abnormal VEP may not be helpful. However, a normal VEP is reassuring. Tubular visual fields done at 1 and 3 m are also commonly seen in functional visual loss. Before pronouncing a patient's visual loss functional, be sure to either use a pinhole to "refract" the patient or send them for ophthalmological refraction. In the setting of presumed functional visual loss referral to an ophthalmologist is prudent to be certain that there is no underlying serious ocular pathology. Patients who complain loudly that the testing is uncomfortable, painful, or an otherwise onerous chore are likely trying to get you to stop examining them for fear of being "found out."

A. Approach to a patient with functional visual loss.

1. Document every visual test performed and the patient's response. This documentation should include their behavior: how they entered the examining room, how they found the chair and sat down, how they regard the examiner, and how much resistance is put up to testing.
2. The greater the resistance to examination and complaints about the tests, the more likely one is dealing with a deliberate malingerer, whereas the more naive functional patient will gladly go along with the exam regardless of the obvious contradictions in performance behavior.
3. Confronting the patient is fruitless and counterproductive. Gentle suggestion that their vision is "better than the patient thinks it is" and that the patient's vision is likely to improve will reassure all but the hard-core malingerer. Remind them gently but confidently that you have seen this problem before and it gets better by itself. Malingerers commonly will accuse the examiner of not believing that their symptoms are real or that they are simply "all in their mind."
4. Radiographic and/or electrophysiologic studies (ERG and VEP) should be done and interpreted for the patient to be sure that no nagging doubts remain. The patient should be told that there is no disease of the central or peripheral nervous system that has been identified. Be sure to do a Schirmer test to identify dry eyes.
5. Do not prescribe eye drops or any medication or refer the patient to a psychiatrist. Prescriptions for medication, glasses, and drops give a double message, that is, "nothing is wrong but take this medication" and psychiatric referrals for functional problems do not produce any more useful results than simple reassurance and encouragement. If they are found to have dry eyes, normal saline drops are reasonable. Explain why you are giving drops.

B. General rules for referral of patients who complain of any kind of visual loss.

1. If the patient has seen a number of eye care specialists (optometrists and ophthalmologists) and continues to complain of visual loss, consider the conditions listed in Table 10.2.
2. Do imaging studies with the visual pathways in mind. If the visual loss is monocular, look at the orbit and intracranial optic nerve. If there is monocular central visual field loss, always test the superior temporal field of the other eye. If the visual loss is bitemporal, look at chiasm and perichiasmal structures.
3. Enlist an ophthalmologist for a computed visual field examination if the patient has not yet had one. Ask for visual fields to be done and for an interpretation of the findings. If the optic disc looks abnormal or the fundus is abnormal, ask for photographs to be taken. As physicians, we always get chest X-rays for lung disease, and we should obtain fundus photos where there is suspected optic nerve or retinal disease. Remember that an ophthalmologist will be able to identify refractive, corneal, lenticular problems as well as vitreous and retinal causes of visual loss.

Recommended Readings

Barton JJ, Corbett JJ. Neuro-ophthalmologic vascular emergencies in the elderly. *Clin Geriatr Med*. 1991;7:525–548.

Bernstein EF, ed. Clinics in Geriatric Medicine. W.B. Saunders Co. Philadelphia. *Amaurosis Fugax* New York. Springer-Verlag; 1988.

Bruno A, Barton JJ, Corbett JJ, et al. Transient monocular visual loss patterns and underlying vascular abnormalities: a prospective study of 100 consecutive patients. *Stroke*. 1990;21:34–39.

Cooper SA, Murray KL, Heath CA, Will RG, Knight RS. Isolated visual symptoms at onset in sporadic Crutzfeldt-Jakob disease: the clinical phenotype of the "Heidenhain variant." *Br J Ophthalmol*. 2005;89:1341–1342.

Hupp SL. Syndromes of the optic chiasm In: Tusa RJ, Newman SA, eds. *Neuro-Ophthalmological Disorders: Diagnostic Workup and Management*. New York, NY: Marcel Dekker; 1995:65–75.

Hupp SL, Kline LB, Corbett JJ. Visual disturbances of migraine. *Surv Ophthalmol*. 1989;33:221–236.

Lee AG, Martin CO. Neuro-ophthalmic findings in the visual variant of Alzheimer's disease. *Ophthalmology*. 2004;111:376–380.

Liu GT, Volpe NJ, Galetta SL (Eds). Disorders of higher cortical visual function. In: *Neuro-ophthalmology Diagnosis and Management*. 2nd ed. Saunders Elsevier; 2010:339–362.

Rizzo M, Nawrat M. Human visual cortex and its disorders. *Curr Opin Ophthalmol*. 1993;4:30–37.

Thompson HS. Functional visual loss. *Am J Ophthalmol*. 1985;100:209–213.

Thompson HS, Corbett JJ. Swinging flashlight test. *Neurology*. 1989;39:154–156.

Trobe JD, Acosta PC, Krischer JP, Trick GL. Confrontation visual field techniques in the detection of anterior visual pathway lesions. *Ann Neurol. 1981*;10:28–34.

Xhang X, Kedar S, Lynn MJ, et al. Homonymous hemianopias. Clinical anatomic correlations in 904 cases. *Neurology*. 2006;66:906–910.

CHAPTER

11 Approach to the Patient with Abnormal Pupils

Aki Kawasaki

The **pupillary light reflex** is composed of an afferent limb and an efferent limb (Fig. 11.1). The afferent limb signals pupillomotor information from the retina to the dorsal midbrain. Except at the brachium of the superior colliculus and pretectal olivary nucleus, **injury along the afferent limb of the pupil light reflex also** results in some form of accompanying visual loss and in unilateral or asymmetric bilateral lesions, a relative afferent pupillary defect (RAPD) will be detected.The efferent limb of the pupil light reflex carries pupilloconstriction signals originating in the Edinger–Westphal subnucleus to the iris. **Injury along the efferent limb** causes mydriasis of the ipsilateral pupil and poor pupillary constriction to all forms of stimulation—direct light, consensual light, or near effort. (See the section on Unilateral Mydriasis.)

Pupillary dilation is a reflex response to sudden arousal or darkness and is mediated by the sympathetic pathway (Fig. 11.2). The pupil size at any moment is determined by the sum input of sympathetic and parasympathetic activity to two iris muscles, the radial dilator, and the sphincter.

I. PUPILLARY EXAMINATION

A. Hippus. An awake patient sitting quietly in room light may show small spontaneous oscillations of pupil size, known as *hippus*. It reflects fluctuations in the modulating signals to the Edinger–Westphal subnuclei.

B. Pupil size. Resting pupil size is greatest during the teenage years and then gradually decreases with increasing age. Asymmetry of pupil size of 0.4 mm or more is visible to the unaided eye and called anisocoria. When present, anisocoria should be measured in darkness and under bright light.

1. Anisocoria that is greater in magnitude under bright light implies a deficit of constriction, thus, the larger pupil is faulty.
2. Anisocoria that is more apparent in darkness or dim light implies a failure of dilation, thus, the smaller pupil is faulty.

C. Pupillary response to light. Have the patient fixate on a distant target in a darkened room. Shine a bright focal light (a nonhalogen penlight is not bright enough) directly onto 1 pupil for 3 seconds and record the amplitude and velocity of constriction. Do this for each pupil 2 or 3 times for a mental "average." Reminder: Simply noting that a pupil is "sluggish" or "responds poorly" to direct light stimulation is not enough information to differentiate an afferent from an efferent pupillary defect. Proceed to the alternating light test to distinguish an afferent pupil defect and check the pupil near response, which should be equally sluggish in the event of an efferent defect.

D. Alternating light test. This is the standard clinical technique for identifying asymmetry of afferent pupillomotor input between the 2 eyes, referred to as the relative afferent pupillary defect (**RAPD)**.The patient usually has subnormal vision in the eye with an RAPD.

1. **Technique.** Have the patient fixate a distant target in a dark room. Shine a bright focal light directly onto 1 pupil for 3 seconds, then quickly swing the light onto the other pupil for 3 seconds. Repeat this for 4 or 5 alternations of light stimulation and watch only the illuminated pupil (direct light response). The amplitude and velocity of pupillary constriction as well as the degree of redilation that occurs within the 3 seconds of light stimulation should be symmetric between the 2 eyes.

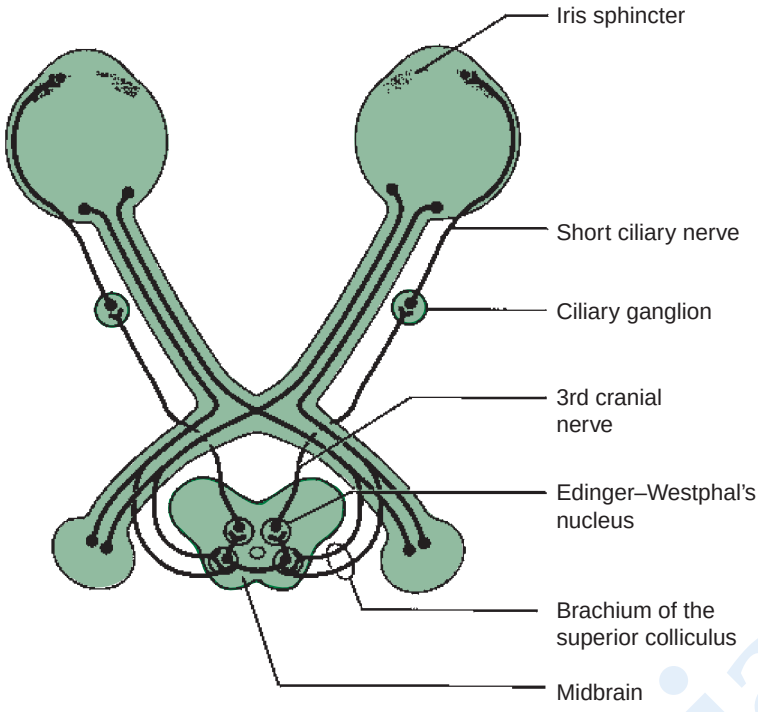


FIGURE 11.1 Schematic diagram of the pupillary light reflex. The afferent limb originates in the retinal photoreceptors that convert light energy to a neural signal. Pupillary information is conveyed from the eye to the brain by the melanopsin-expressing retinal ganglion cells and their axons project to the dorsal midbrain, synapsing in the pretectal olivary nucleus. Each pretectal olivary nucleus distributes the afferent pupillary impulses to the ipsilateral and contralateral Edinger–Westphal subnucleus of the oculomotor nuclear complex. The neurons of the Edinger–Westphal subnucleus initiate the efferent limb of the pupillary light reflex, that is, pupilloconstriction. Efferent pupillomotor impulses travel in the parasympathetic fibers of the oculomotor nerve, synapse in the ciliary ganglion of the orbit, and then pass via the short ciliary nerves to innervate the iris sphincter muscle. (Reprinted with permission from Trobe J. *The Neurology of Vision*. New York: Oxford University Press; 2001.)

2. **A large RAPD** is present if the pupil of the "bad" eye dilates when the light is alternated back onto it after being on the "good" eye. In other words, the bad eye sees so much less light, compared to the good eye that reflex dilation occurs.
3. **A small-to-moderate RAPD** is sometimes difficult to detect. The bad eye generates enough afferent input to initiate pupillary constriction to direct light but it is a less vigorous response compared with that of the good eye. The pupil of the bad eye also "escapes," that is, redilates sooner after the initial constriction.

II. RELATIVE AFFERENT PUPILLARY DEFECT

The presence of an RAPD is a sensitive indicator of unilateral or asymmetric injury to the afferent limb of the pupillary light reflex. If an RAPD is found, it needs to be investigated.

A. Ocular and retinal lesions.

1. Large unilateral retinal lesions such as central retinal artery occlusion or trauma produce an obvious RAPD. Visual acuity is generally poor. A dilated funduscopic examination usually provides the diagnosis.

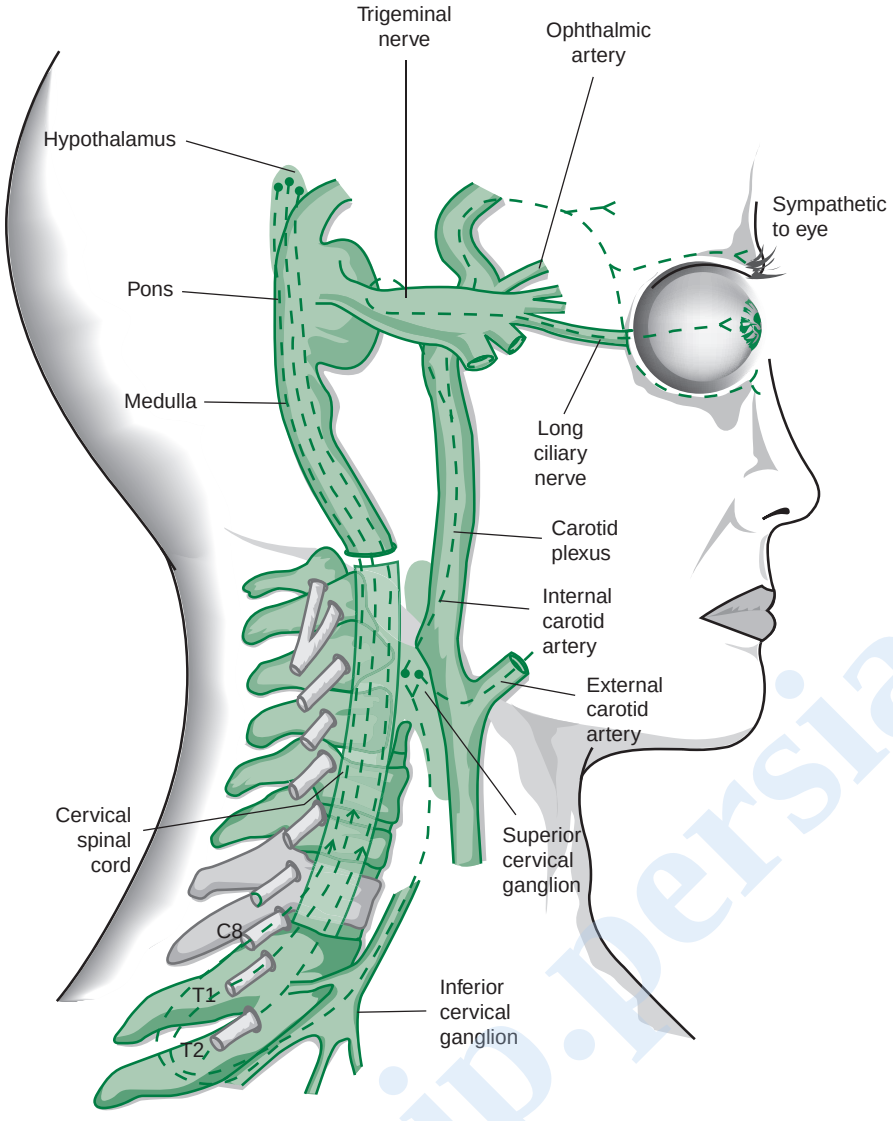


FIGURE 11.2 Schematic diagram of the sympathetic innervation of the pupil and eyelids. First-order hypothalamic (central) neurons descend through the brain stem and cervical spinal cord. These fibers synapse at the ciliospinal center of budge whose cell bodies lie in the intermediolateral gray column and whose axons exit the cord ipsilaterally at C8, T1, and T2 via the ventral roots.These second-order (preganglionic) fibers travel rostrally via the sympathetic chain, traverse the superior mediastinum, pass through the stellate ganglion and terminate in the superior cervical ganglion. The postganglionic axons ascend as a plexus intimately associated with the internal carotid artery to reach the cavernous sinus.The pupil fibers briefly join the sixth nerve then follow branches of the first division of the trigeminal nerve and the long ciliary nerve to reach the iris dilator muscle. Fibers to the tarsal muscles (Muller's muscles) also travel within the carotid plexus to the cavernous sinus then may join branches of the third nerve before reaching the upper and lower eyelids. Sudomotor fibers, e.g., for sweating to the lower face, follow the external carotid and then the facial arteries. (Reprinted with permission from Liu GT, Volpe NJ, Galetta SL. *Neuro-ophthalmology: Diagnosis and Management*. Philadelphia: WB Saunders; 2001.)

2. Cataracts, corneal opacities, and vitreous lesions do not cause an RAPD, even when the visual loss is severe.

B. Optic nerve lesions.

1. Damage to the optic nerve almost always produces an RAPD and an accompanying visual field defect. Loss of acuity is variable.
2. The extent of damage in bilateral optic nerve disorders is rarely symmetric. Therefore, an RAPD is found on the side with greater damage. Look carefully.

C. Optic chiasm. Lesions of the optic chiasm that produce bilateral but asymmetric visual dysfunction cause an RAPD in the eye with greater field loss.

D. Optic tract lesions. Due differences in the retinal sensitivity between the nasal and temporal hemifields, a unilateral optic tract lesion can produce a small RAPD in the contralateral eye. Consider an optic tract lesion in any patient with complete homonymous hemianopsia and an RAPD in the eye with the temporal field loss.

E. Pretectal nucleus. A unilateral dorsal midbrain lesion such as stroke or tumor that damages the pretectal olivary nucleus on one side can produce a small RAPD in the contralateral eye in the absence of visual loss. This is a rare occurrence.

III. MECHANICAL ANISOCORIA: "OPHTHALMOLOGIC" ANISOCORIA

Two iris muscles modulate pupil size and shape—the sphincter and the dilator. Damage to one or both iris muscles can distort the size, shape, and mobility of the pupil. Ocular pathologies such as trauma, infection, or surgery are common causes of a mechanical anisocoria. It is important to consider and identify ocular causes of anisocoria in order to avoid unnecessary neurologic evaluation.

A. History. Inquire about any previous infection, inflammation, trauma, or surgery involving the eyes, including laser procedures.

B. Examination.

1. Marked irregularity of the pupillary margin, unusual distortion of pupillary shape, and a difference in iris color are structural iris defects that may be appreciated with direct observation.
2. A slit lamp examination of the iris is needed to identify most other causes of mechanical anisocoria such as synechiae (adhesions), small sphincter tears, transillumination defects, and inflammation. A dusting of iris pigment may be observed in a ring on the lens of a patient who has had a blow to the eye.

IV. UNILATERAL MYDRIASIS: NEUROLOGIC OR PHARMACOLOGIC?

Once mechanical causes of anisocoria are ruled out, the next obvious step is to check the light reflex of both pupils. If the larger pupil constricts poorly to a bright light compared with the smaller pupil, then the larger pupil is the abnormal pupil. The neural pathway that mediates pupilloconstriction is the oculo–parasympathetic pathway. The preganglionic parasympathetic pupil fibers originate in the Edinger–Westphal subnucleus of the oculomotor and synapse in the ciliary ganglion of the orbit. The postganglionic parasympathetic pupil fibers are carried in the short ciliary nerves to innervate the iris sphincter and ciliary muscle. The neurotransmitter at the iris sphincter is acetylcholine. Three common nonocular conditions causing a large, poorly reactive pupil are oculomotor nerve palsy, a tonic pupil, and a pharmacologically dilated pupil.

A. Oculomotor (third cranial) nerve palsy. Lesions that damage the pupillary fibers of the oculomotor nerve nearly always damage one or more motor fibers of the oculomotor nerve as well. With rare exception, a large poorly reactive pupil that appears as an isolated finding is **NOT** an oculomotor nerve palsy.

1. **Clinical features.**
   a. **Large poorly reactive pupil.** The pupil constricts poorly to light stimulation and near effort.
   b. **Responsiveness to pilocarpine.** The pupil on the side of an oculomotor palsy will constrict vigorously to topical full-strength (1% to 4%) pilocarpine. It can also constrict in response to dilute 0.125% pilocarpine due to cholinergic denervation supersensitivity.
   c. **Ipsilateral ptosis.** The ptosis may range from a barely noticeable ptosis to complete ptosis.
   d. **Ocular motility disturbance.** A deficit of infraduction, supraduction, and/or adduction is nearly always present on the side of the larger pupil. **Caution:** Sometimes only one or two motor functions are disturbed, for example, an oculomotor nerve palsy with only ptosis and supraduction deficit. Crosscover or red glass testing is important for detecting subtle ophthalmoplegia.
2. **Etiology of oculomotor nerve palsy.** **See Table 11.1 and Chapter 12.**
3. **Work-up.** An acute and isolated oculomotor nerve palsy with pupillary involvement warrants emergent neuroimaging to look for pituitary apoplexy, brainstem stroke, or expanding posterior communicating artery aneurysm. Remember that early compression by an aneurysm can cause a partial oculomotor palsy without pupillary dysfunction. Investigation of other causes of an oculomotor nerve palsy should be directed by the clinical presentation.

B. Tonic pupil (Adie pupil). A tonic pupil is the most common neurologic cause of unilateral mydriasis in an otherwise healthy and alert patient. It is caused by a lesion of the ciliary ganglion in the orbit or the postganglionic short ciliary nerves.

1. **Symptoms** are anisocoria, photophobia, blurred near vision, and brow ache.
2. **Clinical features (Fig. 11.3).**
   a. **Large pupil.** A very fresh tonic pupil is a denervated pupil. It is often very dilated and quite unreactive to light stimulation and near effort.
   b. **Poor light reaction.** The pupil light reflex is absent or reduced and never recovers.
   c. **Light-near dissociation (LND).** In the acute stage, the pupillary constriction to near effort is absent. Later, aberrant reinnervation restores the near response and LND becomes apparent. Additionally, the pupillary constriction to near effort is delayed and slow and sustained, hence the term "tonic."
   d. **Pupillary redilation** after a near effort is similarly slow, owing to the tonicity of pupilloconstriction.
   e. **Accommodation paresis**. Accommodation, like the pupillary near response, is lost in the acute phase and later recovers.
   f. **Sectoral palsy of the iris sphincter**. A slit-lamp is usually necessary to detect sectoral sphincter palsy. The areas of sphincter with preserved innervation contract and tighten the pupillary margin like a pulled purse string, but the denervated segments (palsied) are immobile and the adjacent pupillary margin remains flat.
3. **Pharmacologic testing for cholinergic denervation supersensitivity.**
   a. Place 2 drops of dilute pilocarpine (0.125% or less) in each eye. Wait 30 to 45 minutes.
   b. Dilute pilocarpine usually has no effect on a normal eye. Constriction of the suspected pupil is a positive test and indicates denervation of the iris sphincter (Fig. 11.4).
   c. Patients with oculomotor nerve palsy and patients with tonic pupil may demonstrate cholinergic denervation supersensitivity.
4. **Pathophysiology.**
   a. **Acute denervation.** Injury to the ciliary ganglion or short ciliary nerves denervates the ciliary muscle and its sphincter; thus, accommodation and pupilloconstriction are acutely abolished.
   b. **Aberrant reinnervation**. Neurons originally destined for the ciliary muscle for accommodation resprout and appropriately reinnervate the ciliary muscle. In addition, they mistakenly send collateral branches to the iris sphincter (aberrant reinnervation). During the reinnervation phase, accommodation improves and a tonic pupilloconstriction to a near effort develops.

TABLE 11.1 Common Lesions Along the Oculo-parasympathetic Pathway That Cause a Large, Poorly Reactive Pupil

Preganglionic: Oculomotor Nerve Palsy	Postganglionic: Tonic Pupil
Brainstem (midbrain)—"fascicular" Ischemia Hemorrhage Tumor Arteriovenous malformation	**Intraorbital** Viral ganglionitis Trauma Ocular surgery Tumor
Interpeduncular fossa, subarachnoid space Basilar artery aneurysm Basal infection (granulomatous meningitis, fungal meningitis) Intraneural ischemia—"vasculopathic" (e.g., diabetes, hypertension)	**Systemic autonomic neuropathy** **Hereditary neuropathy** (e.g., Charcot–Marie–Tooth's disease, Riley–Day's syndrome) **Acquired peripheral neuropathy** (diabetes, alcohol, toxins, amyloid, vasculitis) **Idiopathic** (Adie) tonic pupil
Cavernous sinus, superior orbital fissure Tumor (e.g., meningioma, pituitary adenoma) Inflammation (Tolosa–Hunt's syndrome) Cavernous carotid aneurysm Thrombosis Fistula	

Brainstem "fascicular" oculomotor nerve palsy occasionally occurs as an isolated finding but is more commonly associated with other neurologic deficits (i.e., Weber's, Benedikt's, Claude's, and Nothnagel's syndromes). Vasculopathic oculomotor nerve palsy tends to spare the pupil. Compressive lesions typically involve the pupil.

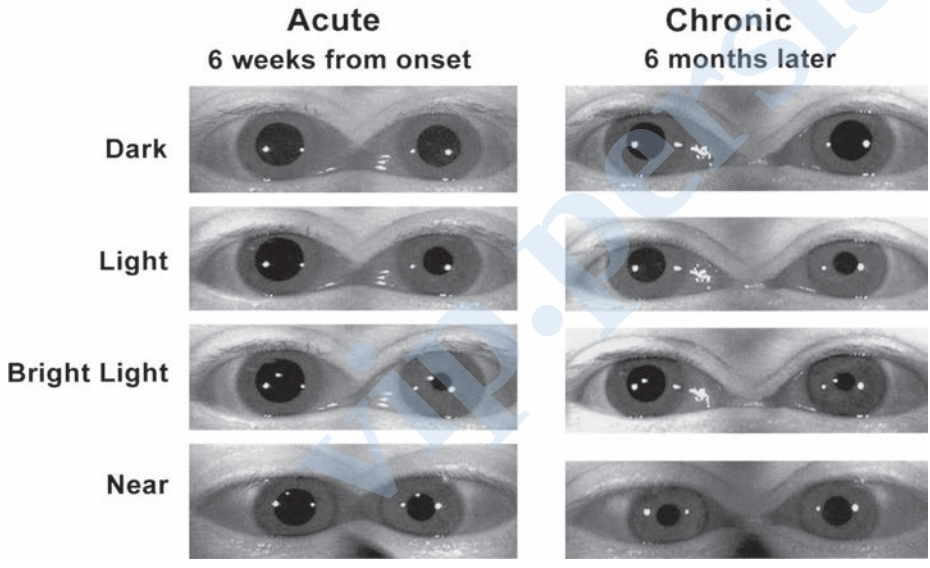


FIGURE 11.3 Patient with a right tonic pupil. Photographs captured from infrared video recording with base out prism to view both pupils simultaneously with high magnification. In the left panel, the patient is seen within 6 weeks of onset of anisocoria. With increasing light, the anisocoria becomes greater because the affected right pupil does not contract to light. A very small contraction to near effort indicates the beginning sign of aberrant reinnervation at this time. In the right panel, the same patient was recorded 6 months later. The right pupil is now a little smaller and is still unreactive to light but does contract to near effort (LND). (Reprinted with permission from Levin LA, Arnold AC, eds. *Neuro-ophthalmology. The Practical Guide*. New York: Thieme; 2005.)

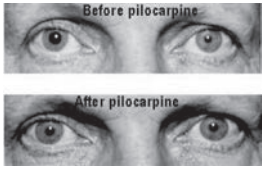
Agent	Mechanism of Action	Test Procedure	Positive Result	Example of Patient with Right Tonic Pupil
Pilocarpine 0.125% or less	Denervation supersensitivity of cholinergic receptors on the iris sphincter to weak cholinergic agonist	Put 2 drops of dilute (0.125%) pilocarpine in both eyes. Wait 45 minutes.	Larger (suspected) pupil becomes smaller pupil Or Suspected pupil constricts more than normal pupil	

FIGURE 11.4 Pharmacologic testing for cholinergic denervation supersensitivity.

5. **Etiology**. (See Table 11.1.) The most common form of an acute unilateral tonic pupil is Adie pupil, an idiopathic condition that typically affects women between the ages of 20 and 40 years. An isolated unilateral tonic pupil does **not** require imaging studies. Bilateral tonic pupils suggest an underlying systemic autonomic neuropathy.

C. Pharmacologic mydriasis (atropinized pupil).

1. Parasympatholytic ophthalmic agents include atropine, scopolamine, homatropine, cyclopentolate, and tropicamide.
2. An atropinized pupil is enormously dilated (8 to 9 mm) and unresponsive to light stimulation and near effort. Sectoral palsy is **NEVER** seen in pharmacologic mydriasis.
3. An atropinized pupil fails to constrict to **full-strength** (1% to 4%) pilocarpine.
4. Other ocular or neurologic findings are absent. There is no history of recent ocular trauma.

V. ANISOCORIA GREATER IN DARKNESS: NEUROLOGIC ANISOCORIA VERSUS PHYSIOLOGIC ANISOCORIA

A. Horner syndrome (an oculosympathetic defect).

1. **Clinical characteristics.**
   a. **Ptosis**. Denervation of the tarsal lid muscles leads to upper lid and lower lid ptosis (elevation of the lower lid). Together they create the impression of enophthalmos. Upper lid ptosis is generally mild and is absent in 12% of patients.
   b. **Anisocoria**. The anisocoria is not marked in room light, often 1.0 mm or less, but becomes more apparent in darkness. As the anisocoria stems from a failure of the smaller pupil to dilate, the light reflex is normal in patients with Horner syndrome.
   c. **Pupillary dilation lag.** Turn the room light off abruptly and watch both pupils. The normal pupil dilates promptly within a few seconds. The Horner pupil dilates slowly, and takes 20 to 30 seconds to reach baseline size in darkness. Pupillary dilation lag is a very specific sign of Horner syndrome but is demonstrable in only about half of patients
   d. **Ipsilateral facial anhidrosis** is variably present.
   e. **Heterochromia iridis** (different iris color) accompanies congenital Horner syndrome.
2. **Pharmacologic diagnosis.**
   a. **Cocaine test**. Cocaine is an indirect sympathomimetic and when placed on the eye, causes pupillary dilation. A sympathetically- denervated (Horner) pupil will not dilate to cocaine. A postcocaine anisocoria of 1.0 mm or greater is considered diagnostic (Fig. 11.5).
   b. **Apraclonidine test.** Apraclonidine has weak α -1 agonist action that can be used to look for adrenergic denervation supersensitivity. A Horner pupil dilates in response to apraclonidine and a reversal of anisocoria is diagnostic (Fig. 11.6).
3. **Localization.**
   a. **Central Horner syndrome** usually is accompanied by other symptoms or signs of brainstem dysfunction (e.g., Wallenberg's syndrome). Anhidrosis involves the whole ipsilateral face, neck, and body.

Agent	Mechanism of Action	Test Procedure	Effect on Normal Eye	Effect on Horner Eye	Positive Result	Example of Patient with Right Horner Syndrome
Cocaine (4% or 10%)	Indirect sympathomimetic via inhibition of the reuptake of norepinephrine in postsynaptic junction	Put 2 drops of cocaine in both eyes Wait 45 minutes	Pupil dilation, lid retraction, conjunctival blanching	None	Postcocaine anisocoria of 1.0 mm or more (smaller pupil is the Horner's pupil)	Before cocaine  After cocaine 

FIGURE 11.5 Pharmacologic testing for Horner syndrome using topical cocaine.

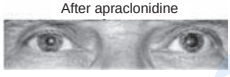
Agent	Mechanism of Action	Test Procedure	Effect on Normal Eye	Effect on Horner Eye	Positive Result	Example of Patient with Left Horner Syndrome
Apraclonidine (0.5% or 1%)	Denervation sensitivity to weak agonist action at postsynaptic alpha 1 adrenergic receptors	Put 1 drop of apaclonidine in both eyes Wait 45 minutes	None	Pupil dilation, lid retraction, conjunctival blanching	Postapraclonidine reversal of anisocoria (larger pupil is Horner' pupil)	Before apraclonidine  After apraclonidine 

FIGURE 11.6 Pharmacologic testing for Horner syndrome using topical apraclonidine.

b. **Preganglionic Horner syndrome** causes ipsilateral anhidrosis of the face and neck only. Weakness and wasting of the ipsilateral hand muscles suggest injury at the C8–T2 spinal rootlets or brachial plexus. Pain in the supraclavicular fossa suggests an superior sulcus lesion (Pancoast's syndrome). A prior history of surgical procedures, such as use of central catheters or thyroidectomy, or trauma to the neck or chest, may identify the cause of oculo-sympathetic injury (Fig. 11.1).

c. **Postganglionic Horner syndrome** is not associated with clinically appreciable facial anhidrosis. Pain in the jaw, ear, throat, or peritonsillar area suggests carotid pathology, particularly dissection. Associated ipsilateral trigeminal dysfunction (dysesthesia, and numbness) or an ipsilateral sixth nerve palsy localizes the lesion to the parasellar–cavernous sinus region of the skull base.

4. **Etiology of Horner syndrome.** In general, a central Horner syndrome is stroke related. Preganglionic lesions are notoriously neoplastic, and postganglionic lesions are mostly benign**. Note: A painful postganglionic Horner syndrome should be evaluated for internal carotid artery dissection**, especially in the acute setting when the risk of stroke is high and anticoagulation may be warranted. Carotid dissection must be differentiated from cluster headaches that can cause postganglionic Horner syndrome in up to 22% of cases.

B. Aberrant regeneration of the oculomotor nerve.

1. **Pathophysiology.** When a structural lesion compresses or transects the oculomotor nerve, the fibers innervating the extraocular muscles can sprout misguided collaterals that aberrantly innervate the iris sphincter. Primary ischemic injury such as diabetic third nerve palsy does not cause aberrant regeneration.
2. **Clinical characteristics.**
   a. **Synchronous unilateral pupilloconstriction** during attempted adduction, supraduction, or infraduction of the globe.This occurs from coactivation of an extraocular muscle and the iris sphincter.
   b. **Poor light reflex.** Because the original parasympathetic fibers to the iris sphincter have been disrupted by the structural lesion, the pupil responds poorly to light and near stimulation.
   c. **Reversed anisocoria.** In some cases, the aberrantly innervated pupil is the larger pupil under bright light and the smaller pupil in darkness.

C. Physiologic anisocoria.

1. This disorder is also called benign or essential anisocoria.
2. **Incidence**. Approximately 20% of the general population has pupillary inequality of 0.4 mm or more in dim lighting.
3. **Clinical characteristics.**
   a. The difference in pupil size is usually 1.0 mm or less and can vary in amplitude (even within a few minutes).
   b. The anisocoria is slightly greater in darkness than in bright light. Patients often notice their anisocoria *disappears* in the sunlight.
   c. Physiologic anisocoria occasionally will *reverse* sides—that is, the larger pupil can be on one side at first but on the other side later.
   d. All reflex pupillary movements are normal and symmetric (light reflex, near response, and dilation in dark). All responses to pharmacologic tests are symmetric.
4. **Work-up.** None.

VI. LIGHT-NEAR DISSOCIATION

Under normal conditions, the amplitude of pupillary constriction to a light stimulus is greater than that to a near effort. Never test the near response with a bright light, because the two stimuli summate and create the false impression of Light-Near Dissociation (LND). LND occurs under the following circumstances.

A. The most common cause of LND is optic neuropathy that results in reduced afferent pupillomotor input.

B. A central lesion may interrupt the afferent signal from the eye (light reflex) but spare the afferent signal mediating the near response. Such a lesion is usually situated in the dorsal midbrain.

1. **Midbrain LND.** This form of LND is a feature of the sylvian aqueduct syndrome or dorsal midbrain syndrome. Both pupils are typically midsize and show poor response to light stimulation. However, the pupil constriction with near effort is normal. Associated motility dysfunction includes bilateral lid retraction, supranuclear vertical gaze palsy, and convergence–retraction nystagmus.
2. **Argyll Robertson pupils.** Both pupils are very small and often irregular in shape.They demonstrate an absence of the light response, a preserved near response as well as poor dilation in darkness. Visual function is intact. Argyll Robertson pupils are distinguished from bilateral chronic tonic pupils (which have LND) by the briskness of the pupil constriction to near effort. In both cases, syphilis must be ruled out.

C. The light response and the near response are initially both damaged, but the near response is restored via aberrant regeneration of the short ciliary nerves. The classic example is a tonic (Adie) pupil.

Recommended Readings

Czarnecki JSC, Thompson HS. The iris sphincter in aberrant regeneration of the third nerve. *Arch Ophthalmol*. 1978;96:1606–1610.

Kardon RH, Bergamin O. Adie pupil. In: Levin LA, Arnold AC, eds. *Neuro-ophthalmology. The Practical Guide*. New York: Thieme; 2005:325–339.

Kardon RH, Denison CE, Brown CK, et al. Critical evaluation of the cocaine test in the diagnosis of Horner syndrome. *Arch Ophthalmol*. 1990;108:384–387.

Kawasaki A. Disorders of pupillary function, accommodation and lacrimation. In: Miller NR, Newman NJ, Biousse V, et al., eds. *Walsh and Hoyt's Clinical Neuro-ophthalmology*. 6th ed. Baltimore, MD: Williams & Wilkins; 2005:739–805.

Thompson HS, Corbett JJ, Cox TA. How to measure the relative afferent pupillary defect. *Surv Ophthalmol*. 1981;26:39–42.

Thompson HS, Kardon RD. The Argyll Robertson pupil. *J Neuroophthalmol*. 2006;26:134–138.

Thompson HS, Kardon RH. Pretectal pupillary defects. *J Clin Neuroophthalmol*. 1991;11:173–174.

CHAPTER

12 Approach to the Patient with Diplopia

Valerie Purvin

Normal binocular vision is accomplished by focusing slightly different views of the same object on the fovea of each eye. When the visual axes are misaligned, the images fall on non-corresponding areas of the two retinas, usually experienced as **diplopia**. Occasional patients interpret this as blurring rather than doubling of the image; the tip-off here is that the "blur" is relieved by closing either eye. Absence of diplopia in the face of misalignment and with intact vision usually implies a very long-standing (often congenital) disorder.

I. MONOCULAR VERSUS BINOCULAR DIPLOPIA

Before embarking on an investigation of diplopia, it is important to determine whether the diplopia is monocular or binocular. For practical purposes, monocular diplopia is always due to some aberration of the ocular media, most often an uncorrected refractive error, corneal aberration, or lenticular change (cataract). Rare cases of monocular diplopia due to neurologic disease, termed "cerebral polyopia," can be identified by the presence of diplopia in both eyes, associated homonymous visual field loss, and other symptoms of disordered visual integration. Finally, unlike monocular diplopia due to ocular disease, cerebral diplopia is not relieved with pinhole. Patients with monocular diplopia should be referred to an ophthalmologist for further evaluation and treatment.

II. HISTORY

A. Description. After establishing that the diplopia is indeed binocular, it is helpful to inquire about some specific spatial and temporal aspects of the patient's diplopia. Is it horizontal or vertical? Is it affected by direction of gaze or by head posture? Is the diplopia worse at distance or at near? Horizontal diplopia at distance (usually prominent when driving) is usually due to sixth nerve palsy (NP) or other source of esotropia. Is the diplopia constant or intermittent? A brief respite from diplopia immediately upon awakening is strongly suggestive of myasthenia gravis; in contrast, more prominence of diplopia with fatigue is nonspecific, frequently described by patients with an underlying phoria that periodically escapes fusion. Has the diplopia changed since onset?

B. Associated symptoms. Patients should also be questioned regarding accompanying symptoms. Is there eye or head pain? The presence of pain with eye movement indicates an orbital condition, usually inflammatory. Pain in the distribution of the first division of the trigeminal nerve (V1) suggests a cavernous sinus/superior orbital fissure localization. Headache in association with sixth nerve weakness is suggestive of increased intracranial pressure (ICP). Other symptoms of increased ICP would include transient visual obscurations and pulsatile tinnitus. Elderly patients with diplopia should be questioned regarding symptoms of giant cell arteritis including scalp tenderness, jaw claudication, and proximal stiffness. In individuals with painless, pupil-sparing diplopia, myasthenia gravis is always a consideration; specific questions would include ptosis, dysphagia, dysarthria, fatigue with chewing, and limb weakness. Finally, patients should be questioned about other symptoms of potential brainstem localization such as dizziness, vertigo, ataxia, numbness, and weakness.

III. TERMINOLOGY

A. We distinguish between a tendency of the eyes to become misaligned, which comes out when binocular viewing is not allowed, termed a **phoria**, and an actual misalignment that is present even with both eyes viewing, termed a **tropia**. Phorias are sometimes referred to as latent deviations, tropias as manifest deviations. Many normal individuals have some degree of underlying phoria that, under normal viewing conditions, is easily held in check by fusional vergence mechanisms. The fusional system is fairly delicate, however, and can be disrupted by a number of factors including advancing age, intercurrent illness, minor trauma, and medications that have CNS depressant properties such as sedative/hypnotics, pain medications, and anticonvulsants.

B. The prefix attached to either term indicates the direction of the manifest or latent deviation: **eso**tropia is an inward deviation of the eye, **exo**tropia outward, **hyper**tropia upward, and **hypo**tropia downward. Common abbreviations used for charting include ET, XT, and HT, with the latter by convention referring to a hyper deviation. **Ortho**phoria indicates that the eyes are aligned.

C. Ocular misalignment may be the same in all fields of gaze, termed **comitant**, or may vary depending on position of gaze, termed **incomitant**. This distinction is important because misalignment that is due to weakness of an extra-ocular muscle is always worse in the direction of action of that muscle whereas nonparetic misalignment (e.g., congenital esotropia) is the same in all fields of gaze. The term **strabismus** is nonspecific, simply referring to any form of ocular misalignment or deviation. Eye movements are usually tested with both eyes viewing, and such eye movements are called **versions**; in some cases it is helpful to observe eye movements in each eye separately (i.e., with just one eye viewing) and these movements are called **ductions**. Infraduction indicates a downward movement, supraduction an upward movement. In vergence movements, the eyes are moving in different directions: convergence (inward movement) and divergence (outward movement).

IV. EXAMINATION

A. Head position and fixation. The first step is to simply watch the patient looking at a target. Patients with a sixth NP often adopt a head turn toward the side of the lesion. A head tilt away from the side of the weak muscle is characteristic of a fourth NP. Such patients often find that their misalignment is better on up gaze (out of the field of the paretic muscle) and so they adopt, in addition, a chin-down posture. Patients with restrictive orbitopathy (e.g., thyroid eye disease) frequently have limitation of up gaze and so will often adopt a head back (chin-up) position. It is normal to have an occasional movement off the fixation target, but the presence of frequent saccadic intrusions indicates loss of normal inhibition of brainstem pause cells and is characteristic of progressive supranuclear palsy and cerebellar dysfunction. Simple inattentiveness to the target causing larger excursions may indicate frontal lobe disease or more global cerebral dysfunction.

B. Range of movement. The patient is instructed to follow a target through the full range of normal eye movements. The range of motion can be quantified using degrees of excursion from primary position, normal being 45° to either side or down and 40° on up gaze or by measuring the amount of scleral show on side gaze. Limitation can also be graded with a series of hatchmarks from 1 to 4 with 1 indicating mild underaction and 4 signifying no movement past mid-position in that direction.

C. Testing saccades. Limitation of eye movement due to cranial NP or supranuclear disorder is associated with saccadic slowing. *In contrast, marked limitation with normal saccadic velocity is characteristic of orbital restrictive disease and of myasthenia.* In the latter, large amplitude saccades may exhibit intrasaccadic fatigue, causing slowing at the end of the excursion. Small amplitude saccades, in contrast, will be quite rapid, sometimes appearing as small "quiver" movements. *Slowing of medial rectus saccades is the most sensitive sign of internuclear ophthalmoplegia* (INO) and is extremely helpful for distinguishing this condition from other causes of adduction deficit.

D. Subjective diplopia testing. Assessment of alignment based on simple observation of the eyes is extremely insensitive, particularly for vertical misalignments. Some information concerning alignment can be obtained from subjective diplopia testing, which includes red glass and Maddox rod techniques, but objective methods are usually more informative. Whatever techniques are used, it is important to note that *the displacement of the image is always opposite to the displacement of the eye*. For example, in esotropia the eyes are turned in (crossed), but the images will appear uncrossed to the patient. When the eye is down, the image is up. Subjective methods are used to identify which image is coming from which eye in order to determine the direction and pattern of misalignment. For example, viewing a small white light with a red glass held over the right eye, a patient with a right sixth NP will report seeing the red light to the right of the white light and will report that the separation of the two images is greater when looking to the right and less when looking to the left. A Maddox rod transforms a point source of white light to a red line and is useful for demonstrating both phorias and tropias, whereas the red glass technique is only applicable to manifest deviations (tropias). This inexpensive and simple device is a valuable addition to the neurologist's set of tools.

E. Objective diplopia testing. Cover tests are the most accurate and preferred method for diagnosing strabismus. In the **cover–uncover test**, one eye is covered and then uncovered while the patient fixates a target first in primary position and then in different positions of gaze. If a tropia is present, when the fixating eye is covered, the other eye will move to reacquire the target. The direction of this movement of redress will always be opposite to the direction of the deviation. For example, if the eye is exotropic, it will move in to take up fixation. In the **alternate (**or **cross-cover) test**, the occluder is quickly transferred from one eye to the other and back, thus preventing binocular viewing. As in the cover–uncover test, any movement of redress is noted. The cover–uncover test reveals tropias, whereas the alternate cover test will demonstrate both tropias and phorias. Although the results of such testing can be quantified with prisms, this aspect of the test is not necessary for obtaining meaningful information.

F. Head-tilt test. Diagnosis of vertical diplopia is notoriously difficult if based on ductional deficits alone. **Bielschowsky's head-tilt test** was designed to determine the paretic muscle responsible for vertical misalignment and is an enormously valuable technique (Fig. 12.1). The measurements that one plugs into the three-step test can be derived from alternate cover testing, red glass, Maddox rod, patient description, or any other technique that provides the necessary information.

Step 1. Note the deviation in primary position. Take, for example, a patient with a right fourth NP (Fig. 12.1). This individual will have a right hypertropia (RHT) in primary position. This pattern could be due to underaction of the superior oblique or inferior rectus muscle in the right eye (not pulling the right eye down sufficiently) or to underaction of the inferior oblique or superior rectus muscle in the left eye (not pulling the left eye up).

Step 2. Record the deviation on gaze to either side. In this case, the deviation is greater on left gaze, indicating that it must be due to a muscle that has its greatest action in that direction of gaze, either the right superior oblique or the left superior rectus.

Step 3. Compare the deviation with tilt to either side. In this case, the deviation is worse with right head tilt. A right head tilt demands an intorsion movement of the right eye,

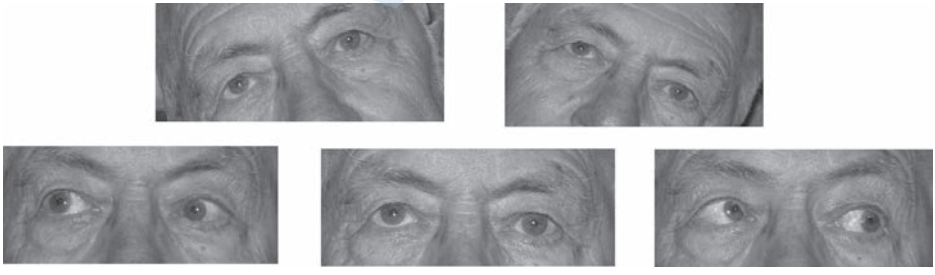


FIGURE 12.1 The three-step test in a patient with a right fourth NP. Note the RHT is greater with left gaze and with right head tilt.

normally accomplished by the superior oblique and superior rectus muscles. The vertical actions of these two muscles normally cancel each other out but, in the face of a weak superior oblique, contraction of the unopposed superior rectus elevates the eye.

G. Other examination features. It is important to look for orbital signs, which are sometimes subtle. These include proptosis, chemosis, conjunctival injection, and globe retraction with attempted eye movement, the latter best observed from the side. Careful inspection for pupil asymmetry or abnormal function is important, particularly in cases of mild or partial third NP. It is also helpful to look specifically and separately for evidence of aberrant regeneration causing third nerve misdirection. Lid abnormalities may be helpful, including both retraction (usually indicative of thyroid eye disease) and ptosis (common in myasthenia, third NP, and oculosympathetic palsy). When eye movements are incomplete with voluntary gaze, it is sometimes helpful to also test reflex movements, either with head turning (the oculocephalic or "doll's head" maneuver), Bell's phenomenon (upward gaze with forced eyelid closure), or calorics.

V. LOCALIZATION AND ETIOLOGIES

Diplopia can be caused by disorders of the brainstem, cranial nerves, extraocular muscles, and orbit. In most cases, the pattern of ocular motor dysfunction and the presence of associated abnormalities will allow accurate localization.

A. Brainstem. Disorders within the brainstem can cause abnormal eye movement by causing nuclear or fascicular cranial NP, INO, and skew deviation. Most lesions that involve **supranuclear** structures do not produce diplopia because reflex input keeps the eyes aligned. The main exceptions to this concept are diseases that affect vergence: divergence insufficiency causes esotropia at distance, and convergence paresis produces exotropia at near. Common causes of brainstem dysfunction are stroke, demyelinating disease, hemorrhage, inflammation, trauma, congenital anomalies, and certain metabolic derangements (e.g., Wernicke's encephalopathy).

1. **Nuclear lesions** cause distinctive patterns of ocular motor dysfunction.
   a. Unilateral lesions of the oculomotor nucleus cause ipsilateral paresis of the EOMs innervated by the third nerve, plus bilateral ptosis and loss of upgaze. The ipsilateral superior rectus subnucleus projects to the contralateral superior rectus causing loss of upgaze in both eyes. Because the levators are innervated by a single midline subnucleus, a unilateral nuclear palsy causes bilateral ptosis.
   b. The trochlear nucleus innervates the contralateral superior oblique muscle. Head trauma, midbrain tumors, and hydrocephalus may damage both fourth nerves because they decussate in the anterior medullary velum.
   c. A lesion of the abducens nucleus produces ipsilateral horizontal gaze palsy rather than a sixth NP because, in addition to motor neurons for abduction, the nucleus contains interneurons that supply the contralateral medial rectus subnucleus.
2. **Fascicular** lesions usually affect adjacent brainstem structures and can be localized accordingly. These syndromes are characterized by an ipsilateral ocular motor NP and contralateral hemisensory or hemimotor deficit and/or ipsilateral cerebellar dysfunction.
3. Damage to the **medial longitudinal fasciculus** produces a disconnection between the ipsilateral abducens nucleus and the contralateral medial rectus subnucleus, resulting in an INO. In addition to a variable degree of ipsilateral adduction deficit, there is slowing of medial rectus saccades and overshoot of contralateral abducting saccades with abduction nystagmus. Despite limitation of adduction, the eyes are usually aligned in primary position. In young patients, the most common etiology is demyelination and INO is commonly bilateral; in older individuals, the cause is most often stroke, and lesions are more often unilateral.
4. Loss of **otolith** input causes vertical strabismus termed **skew deviation**. Unlike misalignment due to cranial NP, the muscle imbalance in skew is typically comitant, that is, the same in all directions of gaze.

B. Cranial nerves. Common causes of cranial neuropathy are ischemia, compression, meningitis (inflammatory or neoplastic), trauma, and congenital. The most common

cause of an isolated ocular motor palsy in older adults is microvascular disease, termed a **vasculopathic palsy**. Most patients have one or more vascular risk factors (diabetes mellitus, hypertension, and hypercholesterolemia). Onset is acute, usually with ipsilateral pain, which resolves spontaneously within 7 to 10 days. Resolution of the motility disturbance takes place within 6 months.

1. **Oculomotor NP** (third NP), when complete, produces an eye that is exotropic and hypotropic with absent adduction and vertical movements, profound ptosis, and a large poorly reactive pupil. Partial forms are often seen and the pattern is sometimes helpful (Fig. 12.2). Loss of upgaze plus ptosis indicates a lesion of the **superior division**. Pupil-sparing third NP is typical of a vasculopathic palsy. In contrast, third NP secondary to a posterior communicating (pCOM) artery aneurysm usually includes early pupil involvement. When third NP is partial, however, the presence of pupil sparing is less reassuring because this pattern is occasionally seen with pCOM aneurysm. An otherwise complete but pupil-sparing third NP is never due to a pCOM aneurysm. Pupil sparing is also common in third NP due to intracavernous lesions.
2. **Trochlear NP (fourth NP)** causes limitation of infraduction when the eye is adducted. Patients report vertical and torsional diplopia. The most common cause is trauma, which frequently produces bilateral fourth NP. Congenital fourth NP is also common and may present at any age due to decompensation of fusion.
3. **Abducens NP** causes esotropia and loss of abduction with slowing of lateral rectus saccades (Fig. 12.3). In young adults, multiple sclerosis and tumors are important considerations. Chronic sixth NP is often due to a compressive lesion at the skull base, such as meningioma. Sixth NP is sometimes a "false localizing sign" of increased ICP.
4. **Combined CN palsy** involving third, fourth, and sixth nerves localizes to the cavernous sinus or superior orbital fissure. The oculosympathetics and first division of the trigeminal nerve are commonly involved. Etiologies include tumor (primary and metastatic), vascular conditions (cavernous sinus thrombosis, fistula, and aneurysm), pituitary apoplexy, and inflammation.

C. Extraocular muscles.

1. **Neuromuscular junction disease** is most commonly due to **myasthenia**, which causes painless, pupil-sparing ptosis and diplopia. Other etiologies include paraneoplastic disease, botulism, and tick paralysis. Myasthenia is characterized by variability and prominent fatigability, often evident in the history and the examination. Symptoms are typically absent upon awakening. Ptosis increases with prolonged upgaze. Myasthenia may affect just a solitary muscle, two or more EOMs or all muscles diffusely. Because of this enormous variability, the disease may mimic a number of different ocular motor conditions, including CN palsies, gaze palsy, and INO. Weakness of eyelid closure as well as eyelid opening is a very helpful finding when present because the levators and the

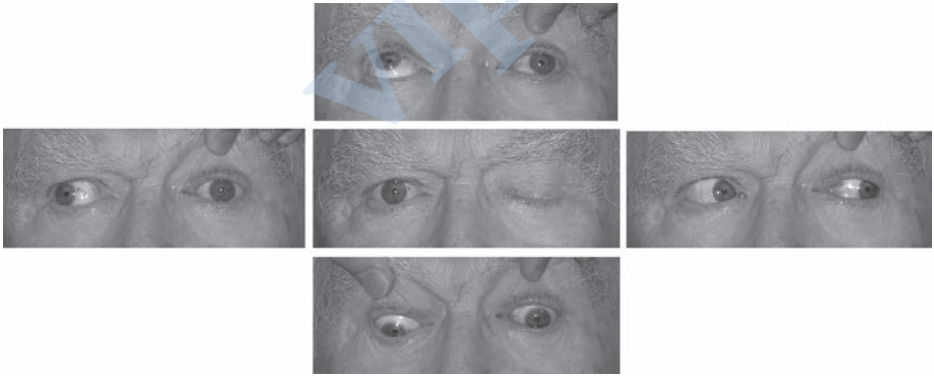


FIGURE 12.2 A 65-year-old man with a diabetic (vasculopathic) left third NP. There is loss of all third nerve function with the exception of the pupil.

orbicularis oculi muscles are innervated by different cranial nerves (third and seventh, respectively).

2. **Chronic progressive external ophthalmoplegia** represents a group of hereditary disorders that causes limitation of eye movements with marked slowing of saccades and ptosis. Most are due to mitochondrial mutations, including Kearn–Sayre, which is sporadic and includes cardiac conduction abnormalities, atypical retinitis pigmentosa, and spongiform CNS changes.
3. **Orbital myositis** is occasionally due to a systemic granulomatous or vasculitic disorder but most commonly occurs as a form of idiopathic orbital inflammatory disease. Acute onset of diplopia is accompanied by pain with eye movement and the diagnosis can be confirmed on neuroimaging.
4. **Graves's ophthalmopathy** causes restriction of eye movements due to inflammatory infiltrates, proliferation of fibroblasts, and edema. The inferior rectus is most commonly affected, producing loss of supraduction. Similarly, involvement of the medial rectus causes loss of abduction, mimicking a sixth NP (Fig. 12.4).
5. **Giant cell arteritis** is an important cause of diplopia in older individuals. Ischemia of extraocular muscles can produce a variety of patterns, sometimes mimicking CN palsy.

D. Orbit.

1. **Masses** in the orbit may displace the globe, mechanically interfere with EOMs, or cause cranial NP. Specific etiologies include primary tumors, vascular lesion, and inflammation including lesions of the paranasal sinuses. Pain, proptosis, chemosis, and conjunctival injection are common.

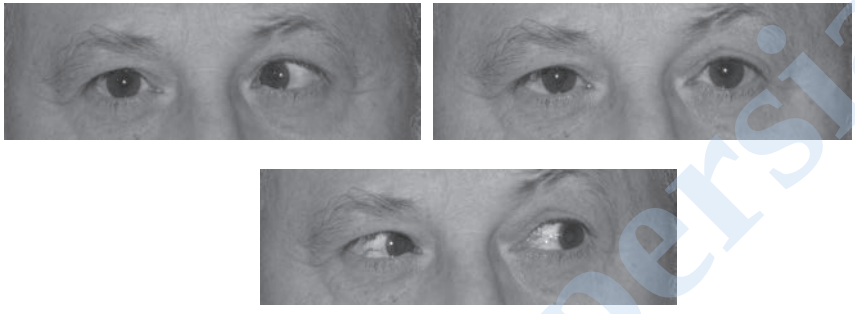


FIGURE 12.3 A 35-year-old man with acute onset of a left sixth NP secondary to multiple sclerosis. There is a moderate esotropia in primary position that increases on left gaze.

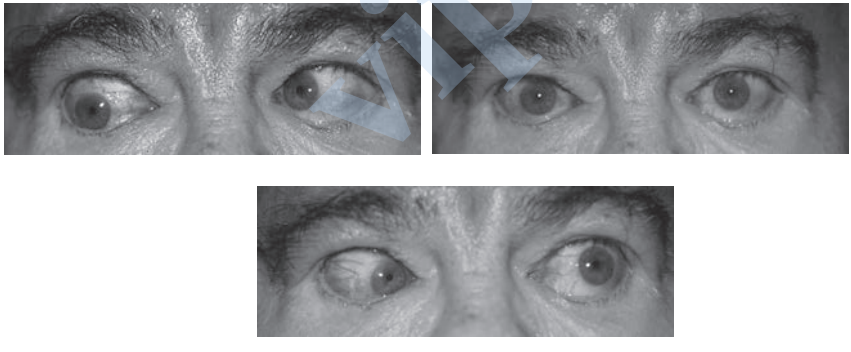


FIGURE 12.4 Esotropia and bilateral abduction deficit in a patient with thyroid eye disease. The presence of bilateral lid retraction and conjunctival injection are helpful signs indicating orbital restrictive disease rather than bilateral sixth NP.

2. Lesions at the **orbital apex** cause a distinctive combination of ipsilateral optic neuropathy and ocular motor disturbance. Because structures are crowded at the back of the orbit, a relatively small lesion can produce severe dysfunction. Small lesions in this area may not be appreciated on neuroimaging, but the clinical findings should point to the correct localization.
3. **Orbital trauma** often causes fracture of delicate orbital bones. A blowout fracture of the orbital floor can cause entrapment of the inferior rectus muscle, producing loss of supraduction. Fracture of the medial wall can entrap the medial rectus, producing an abduction deficit and thus mimicking a sixth NP.

VI. EVALUATION

A. Clinical diagnosis. It is often helpful to start by asking if the diplopia fits the pattern of a cranial NP. In the case of third NP, it is helpful to be able to recognize partial forms; however, it is important to note that isolated weakness of one-third nerve muscle is exceedingly rare. Cases that have this appearance more likely represent myasthenia, INO, or orbital restriction.

In cases in which the diplopia is not consistent with a single cranial NP, pattern recognition becomes extremely important. For instance, loss of supraduction when the eye is abducted is typical of inferior rectus restriction, such as from Graves's disease or orbital floor fracture. Limitation of eye movement and an ipsilateral optic neuropathy constitute the orbital apex syndrome. Any combination of third, fourth, and sixth nerve palsies points to a lesion in the cavernous sinus or superior orbital fissure; there is no other location where these nerves come together. Certain brainstem disorders create distinctive ocular motor patterns. The one-and-a-half syndrome, for example, causes complete loss of conjugate gaze toward the side of the lesion and loss of adduction on the opposite side, leaving intact only abduction away from the lesion. In any patient with painless, pupil-sparing diplopia, the possibility of myasthenia should be considered.

B. Ancillary testing.

1. **Radiographic testing** should be directed to the area of interest determined from the clinical findings. MRI generally provides more information than CT; however, if an orbital process is suspected, it is important to include dedicated fat-suppressed orbit views with gadolinium. Alternatively, CT is an equally effective modality for imaging most orbital structures with the exception of the optic nerve. If optic neuritis is suspected, an MRI is the study of choice.
2. The ideal endpoint for an edrophonium chloride (**Tensilon)** test is a ductional deficit. A small phoria or a subjective judgment by the patient (e.g., "my eyes feel less tired") is unreliable and should be avoided. False negative results are not uncommon; false positives are rare.
3. **Blood tests.** In all elderly patients with diplopia, GCA should be considered. Testing includes CBC, ESR, and CRP. Testing for acetylcholine receptor antibodies is appropriate if myasthenia is suspected, but antibodies are only positive in 30% of patients with the ocular form of the disease. Similarly, thyroid function tests may be normal in patients with thyroid orbitopathy (termed euthyroid Graves's disease).

VII. URGENCY OF EVALUATION

In certain conditions, the clinical outcome depends on timely and appropriate treatment. Prompt recognition of these syndromes is therefore of paramount importance.

A. Aneurysmal third NP. Third NP due to a posterior communicating artery (pCOM) aneurysm usually presents with acute onset of ipsilateral pain and pupil involvement. Most such aneurysms can be identified on good quality MRA or CTA; however, these techniques are not yet 100% accurate, and the degree of accuracy varies among different institutions. If there is a high clinical suspicion of an aneurysm, catheter

angiography should be obtained despite a negative MRA or CTA. This would include patients without vascular risk factors and those with a history suggestive of subarachnoid hemorrhage.

B. Pituitary apoplexy. Hemorrhage or infarction of a pituitary tumor usually causes acute onset of severe headache with symptoms and signs related to meningeal irritation. Visual loss, usually with a bitemporal pattern, and diplopia are common, the latter most often due to third nerve involvement, which may be unilateral or bilateral. In the large majority of cases of pituitary apoplexy, the presence of a tumor was not suspected prior to hemorrhage. The diagnosis is usually apparent on MRI scanning but may be missed with CT, which is usually the most easily accessed radiographic study in an emergency room setting. Prompt diagnosis is crucial because of the potential for acute adrenal insufficiency. Emergency management should include the administration of systemic corticosteroids in stress dosages (e.g., hydrocortisone 100 mg IV every 6 to 8 hours) with careful monitoring of electrolyte balance. Surgical decompression is usually indicated, although occasional patients do well with conservative management.

C. Giant cell arteritis. In any elderly patient with diplopia, the possibility of GCA should be entertained. In addition to inquiring about typical symptoms, an ESR and CRP should be obtained. High-dose steroid treatment should be started upon suspicion of the diagnosis and temporal artery biopsy obtained thereafter.

VIII. TREATMENT

Treatment of diplopia is generally directed toward the underlying condition. In some cases, it is helpful to provide symptomatic relief with prism correction. For diplopia that is expected to be temporary or to change over time, a paste-on (Fresnel) prism is most appropriate; for long-term treatment, a ground-in prism is generally preferred. In cases in which the deviation is too large and/or incomitant to treat with prisms, eye muscle surgery may be undertaken after ocular motility has been stable for a sufficient time period. Diplopia can always be dealt with by patching one eye. In young children, the patch should be alternated to prevent the development of amblyopia; in adults, this is not a concern, and patients are usually most comfortable with the nondominant eye covered.

Recommended Readings

Biousse V, Newman NJ, Oyesiku NM. Precipitating factors in pituitary apoplexy. *J Neurol Neurosurg Psychiatry*. 2001;71:542–545.

Borchert MS. Principles and techniques of the examination of ocular motility and alignment. In: Miller NR, Newman NJ, eds. *Walsh and Hoyt's Clinical Neuro-ophthalmology*. Vol 1, 5th ed. Baltimore, MD: Lippincott Williams & Wilkins; 1998.

Brazis PW, Lee AG. Binocular vertical diplopia. *Mayo Clin Proc*. 1998;73:55–66.

Crane TB, Yee RD, Baloh RW, et al. Analysis of characteristic eye movement abnormalities in internuclear ophthalmoplegia. *Arch Ophthalmol*. 1983;101:206–210.

Jacobson DM, Trobe JD. The emerging role of magnetic resonance angiography in the management of patients with third cranial nerve palsy. *Am J Ophthalmol*. 1999;128:94–96.

Lee AG, Hayman LA, Brazis PW. The evaluation of isolated third nerve palsy revisited: an update on the evolving role of magnetic resonance, computed tomography and catheter angiography. *Surv Ophthalmol*. 2002;47:137–157.

Leigh RJ, Zee DS. *The Neurology of Eye Movements*. Oxford: Oxford University Press; 1999.

Richards BW, Jones FR Jr, Younge BR. Causes and prognosis in 4278 cases of paralysis of the oculomotor, trochlear and abducens cranial nerves. *Am J Ophthalmol*. 1992;113:489.

Weinberg DA, Lesser RL, Vollmer TL. Ocular myasthenia: a protean disorder. *Surv Ophthalmol*. 1994;39:169–210.

Yee RD, Whitcup SM, Williams IM, et al. Saccadic eye movements in myasthenia gravis. *Ophthalmology*. 1987;94:219–225.

CHAPTER

13 Approach to the Patient with Facial Numbness

Betsy B. Love and Marianna R. Beattie

Isolated facial numbness often is descriptive of impairment of sensation of the face as a result of dysfunction of the trigeminal system or central trigeminal pathways.

A. Patients may report unilateral or bilateral facial numbness, paresthesia (a spontaneous abnormal sensation), or dysesthesia (an unpleasant abnormal sensation produced by normal stimuli). There may be associated symptoms of altered sensation of the mucous membranes of the nose, mouth, gums, palate, or teeth. Facial numbness may be a part of a syndrome involving other cranial nerves, in addition to the trigeminal nerve. Trigeminal nerve dysfunction associated with pain is discussed in Chapter 14.

B. Types. The types of facial numbness discussed in this chapter include conditions that may present with isolated facial numbness, including lesions of the trigeminal nerve branches (e.g., trauma, tumor, and connective tissue diseases), the gasserian ganglion (GG) or root (e.g., infection, tumors, and nontumorous masses), and the central trigeminal pathways (e.g., stroke, tumor, and vascular anomalies). Facial numbness is an uncommon, but not rare, condition. A patient with facial numbness may see a dentist, primary physician, neurologist, or otolaryngologist. The typical clinical scenario is gradual onset of numbness in one or more regions of the face, usually unilaterally. Because the presence of facial numbness can indicate a serious underlying condition, each patient with this symptom needs a thorough evaluation.

C. Facial numbness as a symptom of a life-threatening disorder. Facial numbness can represent not only a serious underlying condition that needs to be evaluated expeditiously but also, in some rare instances, a medical condition that must to be dealt with as an emergency. In rare instances, facial numbness is the presenting sign of internal carotid artery dissection, carotid aneurysm, intracranial hemorrhage, or intracranial or nasopharyngeal tumor. However, in most instances, associated features point to one of these serious etiologic conditions. If there are features suggestive of carotid artery dissection or intracranial aneurysm, **appropriate studies may include emergency CT or MRI of the brain and a vascular imaging study (helical cervical CT angiography, MRI/MRA, or conventional cerebral angiography),** depending on the area of concern. MRI of the head with contrast medium is indicated if there is suspicion of an intracranial tumor. Brain CT without contrast material is indicated if intracranial hemorrhage is a concern. An otolaryngology consultation should be obtained if symptoms suggest a nasopharyngeal tumor.

I. ETIOLOGY

A brief review of the trigeminal pathways is necessary for an understanding of the location of dysfunction with facial numbness.

A. Neuroanatomy of the trigeminal nerve.

1. The trigeminal nerve (cranial nerve V) is a mixed sensory and motor nerve.
   a. The sensory portion of the nerve is the largest portion, transmitting sensation from areas of the face, oral cavity, and nasal passages.
   b. There are three divisions of the **sensory portion** of the trigeminal nerve (Fig. 13.1).
      (1) **Ophthalmic (V1).** The ophthalmic division provides cutaneous supply to the forehead and anterior scalp to approximately the vertex, parts of the nose and the upper eyelid, and the upper half of the cornea. Branches of this division to the facial structures are the nasociliary, infratrochlear, supratrochlear, lacrimal, and supraorbital nerves.

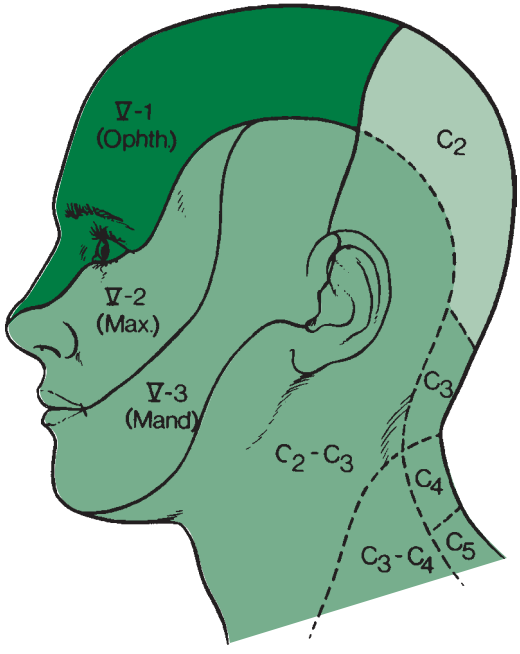


FIGURE 13.1 Regions of the face supplied by the three sensory divisions of the trigeminal nerve (V1, V2, and V3). (Modified from Sears ES, Franklin GM. Diseases of the cranial nerves. In: Rosenberg RN, ed. *Neurology*. New York: Grune & Stratton; 1980, with permission.)

(2) **Maxillary (V2).** The maxillary division provides cutaneous supply to portions of the nose, upper lip, cheek, lower half of the cornea, upper gums and teeth, palate, and nasal mucosa. Branches of this division are the zygomaticofacial, zygomaticotemporal, and infraorbital nerves.

(3) **Mandibular (V3).** The mandibular division provides cutaneous supply to the lower lip; chin; portions of the jaw, ear, and mouth; lower gums and teeth; and the anterior two-thirds of the tongue. Branches of this division are the auriculotemporal, buccal, and mental nerves. The combined nerve trunk of the mandibular division and the motor portion gives rise to the inferior alveolar nerves and the lingual nerves.

c. The **motor portion** of the trigeminal nerve is a smaller division that travels with V3. It provides motor function to the muscles of mastication and the tensor tympani. This portion is not discussed further. However, it is important to examine the patient for dysfunction of the motor portion of the nerve.

2. The three sensory divisions (V1, V2, and V3) enter the cranial cavity through the superior orbital fissure, foramen rotundum, and foramen ovale, respectively, to unite in the gasserian or semilunar ganglion, which lies at the apex of the petrous bones.
3. Second-order sensory neurons enter the pons at the sensory root.

B. Localization of the lesion with facial numbness (Table 13.1). Facial numbness usually is unilateral and can be partial or total. Complex facial numbness is numbness associated with other cranial nerve or brainstem findings. Bilateral numbness can be associated with brainstem involvement, leptomeningeal disease, or systemic diseases, or it can be idiopathic. There are some generalizations that help localize the lesion.

1. Lesions of the divisions of cranial nerve V have distinct areas of sensory loss (Fig. 13.1).
2. Lesions proximal to the GG cause cutaneous numbness of the entire face and the anterior scalp (Fig. 13.2).

TABLE 13.1 Types of Numbness Associated with Lesions in Different Areas of the Trigeminal Sensory System

Location of Lesion	Area of Facial Sensory Loss
Ophthalmic (V1) division	Forehead, scalp, nose (except inferolateral), upper eyelid, upper half of cornea
Maxillary (V2) division	Lateral nose, upper lip, cheek, lower half of cornea, upper gums, palate, mucosa of lower nasal cavity
Mandibular (V3) division	Lower lip, lower jaw, chin, tympanic membrane, auditory meatus, upper ear, floor of mouth, lower gums and teeth, anterior two-thirds of tongue
Proximal to GG	Entire face and all structures listed above
Brainstem	Onionskin sensory loss

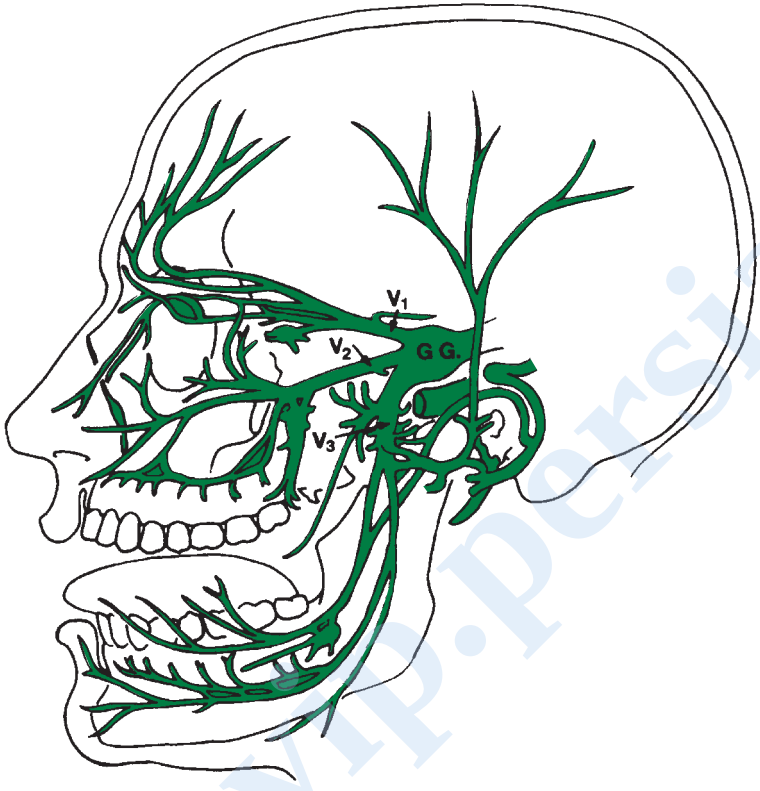


FIGURE 13.2 Relations between the divisions of the trigeminal nerve and the GG.

3. Lesions of the brainstem can produce an onionskin distribution of sensory loss (Fig. 13.3).
4. Lesions of cranial nerve V typically spare the angle of the jaw, which is supplied by C2 and C3 (Fig. 13.1).

C. Causes of facial numbness (Table 13.2). There are many causes of facial numbness. The different causes are discussed according to the known or presumed site of involvement of the trigeminal pathway.

1. **Lesions peripheral to the GG** (V1, V2, and V3).

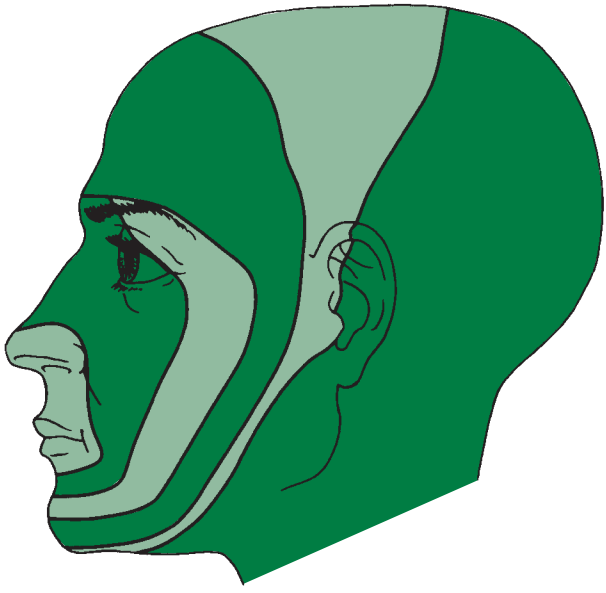


FIGURE 13.3 Onionskin sensory loss resulting from brainstem lesions.

TABLE 13.2 Causes of Facial Numbness[a]

Lesions peripheral to the GG
- Trauma (accidental, dental, and surgical)
- Infection (leprosy, and VZV)
- Systemic diseases (sickle cell anemia, diabetes, and diffuse connective tissue disease)
- Tumor
- Inflammatory
- Drugs or toxins (stilbamidine, cocaine, and others)
- Idiopathic TSN

Lesions of the GG root
- Infection (syphilis, tuberculosis, and VZV)
- Tumor
- Nontumorous mass lesions (aneurysm, and hydrocephalus)
- Sarcoidosis
- Arachnoiditis
- Amyloid
- Drug (trichloroethylene)

Lesions of the central trigeminal pathways
- Stroke
- Tumor
- Syringobulbia
- Demyelinating disease
- Vascular anomaly

[a]Presumed site of pathologic change.

Modified from Hagen NA, Stevens JC, Michet CJ Jr. Trigeminal sensory neuropathy associated with connective tissue disease. *Neurology*. 1990;40:891–896.

a. **Trauma.** Injury to the peripheral branches of the trigeminal nerve can occur with head or facial trauma, dental trauma or surgery, or any surgical procedure on the face (e.g., otorhinolaryngologic or dermatologic surgery).
   (1) **Head or facial injury.** The most frequently affected nerves are the superficial branches, including the supraorbital (branch of V1), supratrochlear (branch of V1), and infraorbital (branch of V2) nerves. The sensory loss is temporally related to the injury. Nerve regeneration can be accompanied by facial pain. The supraorbital branch can be damaged by blunt injury or as a result of a fracture of the upper margin of the orbit. The infra-orbital nerve can be injured with closed head injuries or maxillary fractures. The entire ophthalmic division (V1) can be damaged in fractures through the foramen ovale. Transverse basilar skull fractures can injure the GG, resulting in anesthesia of the entire face and weakness of the masticatory muscles.
   (2) **Dental trauma.** Facial numbness can occur after tooth extraction. The inferior alveolar or lingual nerve can be damaged, and the result is transient anesthesia. Direct nerve injury also can occur as a result of needle trauma during dental anesthesia. In patients with severe mandibular bone resorption, denture use can cause pressure on the mental nerve, resulting in chin numbness.
   (3) **Facial surgery.** Any surgical procedure involving the face can lead to trigeminal nerve injury. Facial numbness has been described as a postoperative complication of microvascular decompression for trigeminal neuralgia due to trauma to the trigeminal root.

b. **Infection**.
   (1) **Leprosy.** Worldwide, lepromatous leprosy is the most common cause of facial numbness. There can be facial hypalgesia and resultant accidental mutilation of the face.
   (2) **Herpes zoster.** Although the herpes zoster virus (VZV) resides in the GG, evidence of active infection usually involves a division of the trigeminal nerve. The most commonly affected division is the ophthalmic division.

c. **Systemic disease.**
   (1) **Sickle cell anemia.** Numbness of the chin and lower lip resulting from mental neuropathy with sickle cell crisis has been described.
   (2) **Diabetes.** Facial numbness has been reported with diabetes and can accompany other forms of sensory neuropathy.
   (3) **Diffuse connective tissue disease.** The presence of facial numbness with a connective tissue disorder is rare. It has been associated with systemic sclerosis, Sjögren's syndrome, mixed connective tissue disease, systemic lupus erythematosus, rheumatoid arthritis, and dermatomyositis.

d. **Tumors.** Regional spread of a tumor along the trigeminal nerve can occur. Disease (most commonly of the lung and breast) metastasizing to the lower jaw can affect the inferior alveolar or mental nerve and cause numbness of the chin and lower lip. Cheek or malar numbness has been described with local spread of tumors along V2 or with leptomeningeal involvement with tumors. Meckel cave tumors (Fig. 13.4) may affect one or more divisions of the trigeminal nerve. Numbness of the cheek or malar region (numb cheek syndrome) may herald the recurrence of squamous cell carcinoma of the skin. Nasopharyngeal tumors (squamous cell carcinoma is most common) arise most frequently in the roof of the pharynx. They can encroach on the trigeminal nerve, producing facial numbness. Associated features can include excessive lacrimation, facial pain, proptosis, hearing loss, and Horner's syndrome.

e. **Inflammatory lesions.** Paranasal sinusitis can affect some branches of the trigeminal nerve.

f. **Drugs and toxins.**
   (1) **Stilbamidine** is an agent that has been used to treat leishmaniasis and multiple myeloma. Unilateral or bilateral facial numbness and anesthesia have been reported after treatment.
   (2) **Cocaine** abuse by the nasal route is a cause of facial numbness in the territory of the maxillary division (V2). Usually there is associated traumatic and ischemic necrosis of the nasal mucosa.

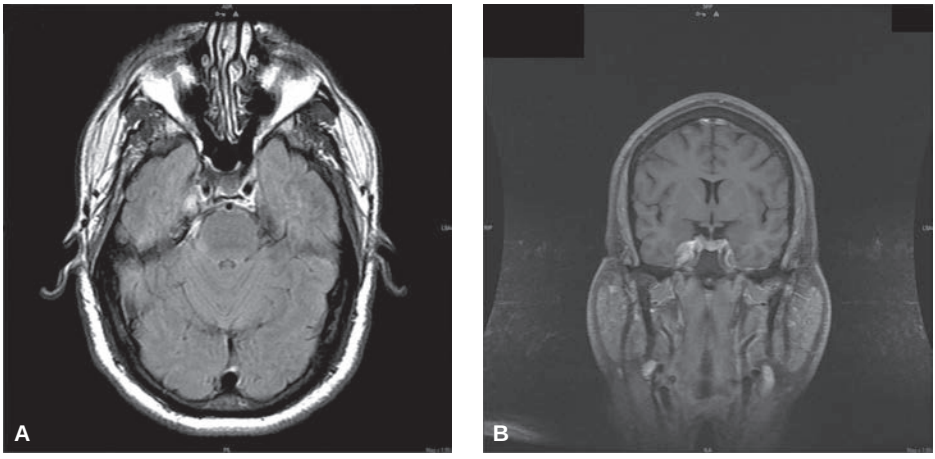


FIGURE 13.4 **A: and B:** Brain MRI with contrast showing enhancing extra-axial mass involving the right Meckel's cave and right cavernous sinus extending into the tentorium. (Courtesy of Drs. Ulises Nobo and José Biller.)

(3) **Other drugs.** Many drugs can cause facial paresthesia. Circumoral paresthesia has been reported with labetalol, and mandibular neuropathy has been reported with allopurinol.

g. **Vascular disorders.** In rare instances, carotid artery dissection can produce facial numbness.

h. **Idiopathic trigeminal sensory neuropathy (TSN).** This diagnosis is one of exclusion after serious causes have been ruled out (see **III**).

2. **Lesions of the GG or root.**
   a. **Infection** of the GG can occur with syphilis, tuberculosis, and herpes zoster.
   b. **Tumor.** Various tumors can affect the GG or root. Tumors that arise in the ganglion (ganglioneuroma or gangliocytoma) tend to have early, associated pain. Tumors that arise primarily in the root (neurinoma or neurofibroma) tend to have predominant sensory loss without pain. Tumors that can compress or invade the ganglion or root include acoustic neuroma, meningioma, schwannoma, cholesteatoma, pituitary adenoma, chordoma, nasopharyngeal carcinoma, and metastatic lesions.
   c. **Nontumorous mass lesions (aneurysm and hydrocephalus).**
   d. **Sarcoidosis.**
   e. **Arachnoiditis.**
   f. **Amyloid.** In rare instances, the GG or root can be the solitary site of amyloid deposits.
   g. **Drug.** Trichloroethylene is an industrial solvent that has been associated with facial numbness.
3. **Lesions of the central trigeminal pathways.**
   a. **Stroke.** Infarction in the lateral tegmentum of the medulla (Wallenberg's syndrome) can produce ipsilateral facial numbness along with other cranial nerve deficits and long tract signs. In rare instances, lateral pontine hemorrhage causes isolated facial numbness, perhaps as a result of involvement of the main sensory nucleus of the trigeminal nerve.
   b. **Tumor.** Tumors of the pons or medulla can affect the sensory nucleus of cranial nerve V, but there are usually other signs, including long tract and cranial nerve findings.
   c. **Syringobulbia.** This central cavitation of the medulla or pons can be associated with facial numbness.

d. **Demyelinating disease.** Facial numbness is the initial symptom in 2% to 3% of patients with multiple sclerosis.
e. **Vascular anomalies.** Isolated facial numbness very rarely results from a posterior fossa aneurysm or other vascular malformation.

II. CLINICAL MANIFESTATIONS

A. Trigeminal sensory neuropathy. The literature is rather unclear in its definition of *TSN*. It has been used to describe different populations of patients with facial numbness. Blau et al. in 1969 described a population of patients with TSN who had self-limited facial paresthesia that in one half of the cases resolved in several months. There were no associated neurologic deficits. At neurologic examination, the corneal response was intact, and the only finding was a subjective decrease in light touch and pinprick over the involved trigeminal distribution. Only 10% of these patients had identifiable causes of TSN, and 10% went on to have trigeminal neuralgia. In contrast to this population, with a seemingly benign course, Horowitz in 1974 found that 88% of a population with facial numbness had an identifiable, usually serious condition. This population almost always had other neurologic deficits (cranial nerve or ataxia). It may be concluded that these two studies involved quite different populations.

TSN is best defined as a general term for facial numbness of which there are many different causes, as previously discussed. Any area of the face can be involved. **Idiopathic TSN** is used to describe purely sensory impairment of unknown causation in a territory of the trigeminal nerve (usually V2 or V3) on one or both sides of the face. It can be associated with pain, paresthesia, or dysfunction of taste. Because the data currently available do not allow one to differentiate consistently between facial numbness that is benign and facial numbness that is attributable to a serious condition, idiopathic TSN remains a diagnosis of exclusion after an appropriate, thorough evaluation. Available data do indicate that the presence of associated neurologic signs and deficits usually points to a more ominous process.

B. Numb chin and numb cheek syndromes.

1. **Numb chin syndrome** is an uncommon form of facial neuropathy. However, the occurrence of this syndrome is notable because in the absence of a history of dental trauma, numb chin syndrome rarely is caused by benign lesions and often is a symptom of more ominous processes such as involvement of the mental or inferior alveolar nerves (branches of V3) by systemic cancer.
   a. Any tumor metastasizing to the jaw can produce this syndrome, but malignant tumors of the breast, lung, and lymphoreticular system are found most commonly. Numb chin syndrome also can be caused by metastasis to the proximal mandibular root at the base of the skull or by leptomeningeal involvement with malignant tumors such as lymphoma.
   b. Most patients already have a known diagnosis of cancer. However, mental neuropathy can be the initial symptom of malignant disease or it can herald tumor recurrence or progression.
   c. The **clinical presentation** involves ipsilateral numbness or anesthesia of the skin and mucosa of the lower lip and chin that extends to the midline. There is usually no associated pain, but there can be lip swelling and ulceration from biting of the numb lip.
   d. The **evaluation** of patients with numb chin syndrome should include radiographs of the mandible with particular attention to the mental foramen, radiographs of the basal skull, MRI of the brain with contrast enhancement, and if there is concern of leptomeningeal infiltration, CSF analysis.
   e. Although a numb chin is a seemingly benign problem, it should be thoroughly evaluated because of its clinical importance as a possible sign of malignant disease.
2. **Numb cheek syndrome.** Lesions of the maxillary division of the trigeminal nerve in the infraorbital foramen may cause the numb cheek syndrome. Unilateral numbness over the malar region and the upper lip in an infraorbital nerve distribution is typical of this syndrome. These findings can have implications similar to those of numb chin

syndrome. Malignancies such as squamous or basal cell carcinoma of the facial skin can spread along the trigeminal nerve. Such tumors also can spread from regional nerves to the skull base and into the intracranial space. Numbness of the anterior gums and teeth suggests a more peripheral lesion, whereas both anterior and posterior gum and teeth involvement suggests leptomeningeal disease.

III. EVALUATION

A. History. It is important to obtain as much detailed information as possible about the patient's facial numbness. The points that should be addressed include the following:

1. **Sites** of numbness, including whether the numbness is unilateral or bilateral.
2. **Duration** of numbness.
3. **Quality** of numbness.
4. **Associated features** (pain, altered taste, and nasal, dental, and cerebrovascular symptoms).
5. History of **trauma** (accidental, dental, or surgical).
6. History of **malignant disease.**
7. **Medications** used currently and in the past.

B. Physical examination.

1. **General physical examination.** A thorough, complete examination is necessary to evaluate for a potential cause of the facial numbness. Particular attention must be paid to evaluating for an underlying malignant lesion (including nasopharyngeal tumor), a dental problem, or an underlying rheumatologic condition. Although many different areas need to be assessed, the following areas are especially important.
   a. **Head and neck.** Inspection of the nose, mouth, and teeth and palpation for adenopathy are important.
   b. **Vascular disorders.** Bilateral blood pressure should be checked to evaluate for vascular disease. Auscultation for carotid or vertebral bruits should be performed. If there is suspicion of an intracranial aneurysm, listen for cranial bruits.
   c. **Breast.**
   d. **Pulmonary.**
   e. **Lymphatic.**
   f. **Rheumatologic.**
   g. **Skin.**
2. **Neurologic examination.** A thorough neurologic examination is necessary. It is particularly important to evaluate all of the functions of the trigeminal nerve and to evaluate for evidence of dysfunction of other cranial nerves.
   a. **Clinical evaluation of the trigeminal nerve.**
      (1) **Sensory evaluation.** Touch, pain, and temperature are tested in the distribution of the three divisions. Each division is tested individually and compared with the opposite side. The sensation in the nasal and oral mucosa, the anterior two-thirds of the tongue, and the anterior portion of the ear (tragus and anterior helix) should be assessed.
      (2) **Motor evaluation.** The motor functions of the trigeminal nerve are assessed by means of testing the muscles of mastication. By having a patient clench the jaw, the strength of the masseters and temporalis can be tested bilaterally. Weakness is evidenced by absent or reduced contraction of the muscles on the side of the lesion. The lateral pterygoids are tested by having the patient move the jaw from side to side against the resistance of the examiner's hand. The jaw deviates toward the paralyzed side on opening the mouth because of contraction of the intact contralateral lateral pterygoid muscle. It cannot be deviated to the opposite, nonparalyzed side. Finally, the patient should be asked to protrude the jaw. Any evidence of atrophy or fasciculation is noted.
      (3) **Reflex evaluation.**
         (a) **Corneal reflex.** This reflex is assessed by means of touching a wisp of a sterile cotton-tipped applicator to the edge of the cornea (not the sclera) bilaterally.

The afferent portion of the reflex is carried by V1 (upper cornea) and V2 (lower cornea), and the efferent portion is carried by cranial nerve VII, both ipsilaterally and contralaterally. Lesions of the trigeminal nerve may cause a diminished or absent response both ipsilaterally and contralaterally.

(b) **Orbicularis oculi reflex (blink reflex).** This reflex is assessed by means of tapping the glabella or supraorbital ridge. This elicits an early ipsilateral blink followed by bilateral blinking.

(c) **Sternutatory reflex.** This reflex is assessed by means of checking light touch sensation of the lateral nasal mucosa with a cotton-tipped applicator. The appropriate response is immediate withdrawal from the irritating stimulus. This reflex may be diminished or absent in lesions of the maxillary division (V2).

(d) **Masseter reflex or jaw jerk.** This reflex is assessed by means of tapping the slightly opened lower jaw. Lesions of the trigeminal nerve may result in a hypoactive ipsilateral jerk, whereas bilateral supranuclear lesions may result in a hyperactive response.

b. **The rest of the neurologic examination.**

(1) **Speech.** Dysarthria may be present with profound facial, tongue, or oral sensory deficits.

(2) **Cranial nerves.** Careful attention should be paid to associated abnormalities of cranial nerves, especially II, III, IV, VI, VII, and VIII.

(3) **Motor and muscle stretch reflexes.**

(4) **Sensory loss.** It is important to evaluate for evidence of other regions of sensory loss, especially generalized sensory neuropathy.

(5) **Coordination.** Coordination can be impaired by a process such as a tumor in the cerebellopontine angle.

(6) **Gait and station.**

C. Laboratory studies.

1. **Biochemical tests** include complete blood cell count with differential, complete chemistry profile including liver function tests and glucose level, and erythrocyte sedimentation rate. In certain situations, a Venereal Disease Research Laboratory test, antinuclear antibody determination, rheumatoid factor, extractable nuclear antigen antibodies, or an angiotensin-converting enzyme level may be necessary. Skin scraping or biopsy is necessary when leprosy is a consideration.
2. **A purified protein derivative test** should be done if there is suspicion of tuberculosis.
3. A **chest radiograph** should be obtained to evaluate for a malignancy, pulmonary disease, or tuberculosis.
4. **Skull and sinus radiography.** A radiograph of the mandible is indicated if there is a numb chin.
5. **Lumbar puncture** is essential if there is suspicion of infection or a malignant tumor of the leptomeninges.
6. A **blink reflex** may be elicited electrophysiologically by means of electrical stimulation of the supraorbital nerve. It can be helpful in detecting subtle central or peripheral lesions of the trigeminal nerve.
7. **Brain imaging.** MRI without and with contrast is the imaging test of choice in most instances. The correct imaging protocol to evaluate the area of the suspected lesion should be discussed with the neuroradiologist prior to the test. CT with and without contrast enhancement may be indicated if MRI is not available or if there are contraindications to MRI.

IV. DIFFERENTIAL DIAGNOSIS

Specific locations of lesion causing facial numbness are detailed in Table 13.1.

A. Tumor.

B. Infection.

C. Trauma.

D. Connective tissue disease.
E. Drug or toxin.
F. Nontumor mass lesion.
G. Vascular disorder.
H. Demyelinating disorder.
I. Other systemic or rare disease.
J. Idiopathic disorder.

V. DIAGNOSTIC APPROACH

A. The first step is to define clinically whether the deficit involves a division or divisions of the trigeminal nerve, the GG or root, or the central trigeminal pathways. Detecting involvement of other cranial nerves or signs of associated diseases can help to limit the number of diagnostic possibilities.

B. Appropriate tests are performed depending on the results of the examination. Unless there is an obvious history of trauma, the following tests should be performed: complete blood cell count with differential, chemistry profile, erythrocyte sedimentation rate, chest radiography, and brain MRI. For selected patients, other tests are indicated, such as Venereal Disease Research Laboratory test, antinuclear antibody determination, extractable nuclear antigen antibodies determination, angiotensin-converting enzyme measurement, purified protein derivative test, blink reflex, lumbar puncture, skull radiography, sinus radiography, and brain CT.

VI. REFERRAL

Because the range of possible underlying diseases that can cause facial numbness is so wide, it is often necessary to use a teamwork approach to this problem. A **neurologist,** who should be most familiar with localization of lesions of the trigeminal nerve, should be consulted initially. It is often necessary to consult an **otolaryngologist** to evaluate for the presence of a nasopharyngeal tumor, acoustic neuroma, or sinusitis. A **dentist** or an **oral surgeon** may be needed to assist in ruling out a dental cause of facial numbness. In selected instances, a **rheumatologist** may be needed if there is evidence of associated connective tissue disease.

Recommended Readings

Bar-Ziv J, Slasky BS. CT imaging of mental nerve neuropathy: the numb chin syndrome. *AJR Am J Roentgenol*. 1997;168:371–376.

Blau JN, Harris M, Kennett S. Trigeminal sensory neuropathy. *N Engl J Med*. 1969;281:873–876.

Brazis PW, Masdeu JC, Biller J. Cranial nerve V (the trigeminal nerve). Chapter 9. In: Brazis PW, Masdeu JC, Biller J, eds. *Localization in Clinical Neurology*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins, Wolters Kluwer; 2011:305–319.

Bruyn RPM, Boogerd W. The numb chin. *Clin Neurol Neurosurg*. 1991;93:187.

Burt RK, Sharfman WH, Karp BI, et al. Mental neuropathy (numb chin syndrome): a harbinger of tumor progression or relapse. *Cancer*. 1992;70:877–881.

Campbell WW. The numb cheek syndrome: a sign of infraorbital neuropathy. *Neurology*. 1986;36:421–423.

Gonella MC, Fischbein NJ, So YT. Disorders of the trigeminal system. *Semin Neurol*. 2009;29:36–44.

Greenberg HS, Deck MD, Vikram B, et al. Metastasis to the base of the skull: clinical findings in 43 patients. *Neurology*. 1981;31:530–537.

Hagen NA, Stevens JC, Michet CJ. Trigeminal sensory neuropathy associated with connective tissue disease. *Neurology*. 1990;40:891–896.

Horowitz SH. Isolated facial numbness: clinical significance and relation to trigeminal neuropathy. *Ann Intern Med*. 1974;80:49.

Janjua RM, Wong KM, Parekh A, et al. Management of the great mimicker, Meckel cave tumors. *Oper Neurosurg*. 2010;67(ONS suppl 2):ons416–ons421.

Kuntzer T, Bogousslavsky J, Rilliet B, et al. Herald facial numbness. *Eur Neurol*. 1992;32:297–301.
Lecky BR, Hughes RA, Murray NM, et al. Trigeminal sensory neuropathy: a study of 22 cases. *Brain*. 1987;110: 1463–1485.
Robinson CM, Addy L, Wylie M, et al. A study of the clinical characteristics of benign trigeminal sensory neuropathy. *J Oral Maxillofac Surg*. 2003;61:325–332.
Sears ES, Franklin GM. Diseases of the cranial nerves. In: Rosenberg RN, ed. *Neurology*. New York: Grune & Stratton; 1980.

CHAPTER

14 Approach to the Patient with Facial Pain

Murray S. Flaster

Facial pain is a frequent presenting complaint in the general clinic, the neurology clinic, and in the emergency department. Age, gender, and a detailed description of the pain complaint and accompanying symptoms will frequently suggest the correct diagnosis, whereas history, neurologic, and general physical examination generate a limited differential to help to further focus the investigation. Not infrequently, the patient has already been seen by several providers, often including a dentist, oral surgeon, or otolaryngologist, and testing and interventions have proved unhelpful. Many of these patients have normal or inconclusive imaging and normal examinations.

In this chapter, we will consider trigeminal neuralgia (TN), both idiopathic (classic) and secondary, the much rarer glossopharyngeal neuralgia (GN), migraine, and the trigeminal autonomic cephalgias (TACs), as well as herpetic and post herpetic neuralgia. Temporomandibular joint (TMJ) dysfunction and atypical facial pain (which has been recently renamed persistent idiopathic facial pain [PIFP]) will be briefly considered. Other causes of facial pain including cranial sinusitis, dental caries, acute glaucoma, and other causes of orbital and periorbital pain, temporal arteritis, and arterial dissections will be briefly discussed.

The practitioner should bear in mind that patients with facial pain, especially those with chronicity are frequently distraught, needy, and often quite complex.

I. TRIGEMINAL NEURALGIA

TN is probably the most common of facial pain disorders, and broadly speaking is among the more severe pain disorders known. Patients complain of very brief, electric-like or lancinating pain involving one or more branches of the trigeminal nerve. Typically the second and third divisions of the trigeminal nerve are involved, contiguously or individually. Rarely, the first division may also be involved, but almost never in isolation. The painful jolt lasts for seconds but can recur multiple times, often in bursts. The pain is almost always unilateral, and its overwhelming severity completely and visibly absorbs the patient when it strikes. Most commonly, there is no pain or paresthesias in between lancinating events and the painful episodes can dissipate as unexpectedly as they appear. The syndrome is often episodic, with painful epochs that stretch for weeks or months, and with spontaneous remissions lasting even years. Over time, typically measured in months or years, there appears to be a tendency toward increasing refractoriness to therapies. Very often, the patient will describe a trigger or aggravating feature that includes talking, chewing, brushing of teeth, application of makeup, shaving, casual contact with the effected area, or even a stimulus as subtle as an air current. Chewing and swallowing presents so much difficulty that the patient loses weight and may even suffer dehydration. The sudden, invasive, and miserable nature of TN is captured by the French phrase *tic douloureux*. In some patients, usually years after symptom onset, pain may become longer lasting with duller, more constant pain supervening together with paresthesias in the affected territory. Patients reporting these more complex pain phenomena may also have less predictable responses to invasive treatment, leading many authors to additionally classify these patients as "atypical TN."

TN is etiologically divided into classic (or idiopathic) and symptomatic. Symptomatic TN may be due to compressive tumor (meningioma, acoustic neuroma, and epidermoid), infiltrative neoplasm, or to an inflammatory process, particularly multiple sclerosis. Other cited etiologies include vascular malformations, brainstem ischemia, facial trauma, and arteritis. Bilaterality strongly implies a secondary cause although most symptomatic TN cases are unilateral. Younger

age favors a secondary cause but classic TN has been described in younger patients. The etiology of classic TN remains uncertain, but most authorities believe that demyelinative damage at the root entry zone due to vascular compression is causal. Neuroimaging studies, specifically MRI may show a secondary cause in up to 15% of cases and at least one neuroimaging study should be encouraged regardless of how typical a patient's presentation may appear. High-field strength, high-resolution diffusion-tensor MR may be able to identify both the offending vessel and intrinsic change within the nerve, and so eventually become a reliable means of confirming classic TN.

TN has a prevalence of 3 to 6 per 100,000 becomes more frequent with age, particularly after age 60 and is nearly twice as frequent in women. Still, there is no completely secure clinical profile unequivocally establishing classical TN. On the other hand, neither involvement of the first division of the trigeminal nerve nor refractoriness to therapy should be considered completely reliable indicators of symptomatic TN. Most importantly, continuous pain or paresthesias or an abnormal neurologic examination prompts a thorough search for a symptomatic cause.

The general recommendation for initial therapy beyond analgesics is oral antiepileptic drug (AED), with carbamazepine most commonly considered first line therapy and where initial favorable response rates in classic TN approach 90%. Treatment with carbamazepine becomes less effective over time, partly due to increased hepatic elimination (autoinduction) but likely involving other, less understood mechanisms. Other agents including oxcarbamazepine, lamotrigine, gabapentin, or baclofen can be effective in monotherapy or as add on therapies. Familiarity with these agents, their side effects, and drug–drug interactions on the part of the treating physician are recommended.

There is general agreement that patients refractory to medical therapy should be considered for surgical intervention although evidenced-based data are sparse and broad agreement on how soon to seek surgical alternatives is lacking. A very effective approach with high rates of immediate pain relief and very effective long-lasting benefit involves craniotomy with microscopic vascular decompression (MVD) at the trigeminal root. High-resolution MRI has been employed to detect these offending vessels and predict successful MVD but reliability of these methods remains incomplete. Perioperative and postoperative complications occur, but are infrequent in the hands of experienced neurosurgeons. Less invasive partial destructive procedures include radiofrequency thermal rhizotomy, done very commonly and percutaneous balloon microcompression and less frequently, chemical rhizotomy. Stereotactic radiosurgery should be considered when patient infirmity or patient preference weighs against open surgery. The percutaneous procedures offer degrees of initial pain relief similar to that of MVD but also modestly less reliable sustained benefit. Complications potentially include deafferentation syndromes (anesthesia dolorosa or corneal hypoesthesia with keratitis) hearing loss or CSF leak. In the case of the least invasive nonmedicinal approach, stereotactic radio surgery, the patient must be made aware that pain relief will not become effective for a mean interval of about 1 month. Many experienced neurosurgeons are of the opinion and that too many patients have suffered for too long before being referred for definitive interventional therapy. The role of invasive therapy in patients with multiple sclerosis remains more controversial.

We stress that interventional procedures are effective in patients with classic TN but in patients with other causes of facial pain or frankly equivocal cases of TN, invasive procedures are wisely avoided or approached with appropriate circumspection.

II. GLOSSOPHARYNGEAL NEURALGIA

GN is similar to TN in that it presents with unilateral lancinating pain involving the posterior-lateral aspect of the throat (tonsil), the posterior aspect of the tongue, the ear, or larynx and as is the case for TN, remains a clinical diagnosis. Swallowing is a typical trigger as are speech or cough. The lancinating pain appears in some patients to trigger a coughing fit. A rare variant accompanied by syncope has been described which through presumed influence on vagus nerve outflow can cause recurrent brady-arrhythmia and even asystole. Like TN, GN may remit or relapse spontaneously but it is a far rarer disorder, with an estimated frequency of between 1/10th and 100th that of TN. It may be either idiopathic or

symptomatic. Symptomatic causes include tumors of the skull base, infection, an expansile vertebral artery due to large atheroma, or malformation of the skull base. Otolaryngologic evaluation as well as neuroimaging evaluation is recommended. Elimination of triggered pain by the application of topical anesthetic may help support the diagnosis. Microvascular compression is considered the underlying cause of idiopathic GN by many authorities and so a surgical approach is often recommended if medical therapy is ineffective. High-resolution MRI lends some support to the theory of microvascular compression. In many cases, severity of GN may be milder relative to TN and in some instances, patient assurance has proved a sufficient remedy.

III. HERPES ZOSTER (HZ) NEURALGIAS

The acute or chronic neuralgia resulting from the segmental (dermatomal) recrudescence of herpes virus in the dorsal root ganglia is quite distinct clinically from TN and is generally readily recognized acutely by a characteristic, topographically distinct, unilateral rash. Because involvement of the trigeminal ganglion in reactivated latent herpes virus infection is common, HZ is a frequent cause of facial pain, especially in the elderly.

HZ has an overall incidence of between 1.5 and 3 per 1,000 annually, but this incidence rises to up to 6.5 per 1,000 by age 60 and up to 11 per 1,000 by age 70. Between 20% and 40% of all individuals will experience HZ in their lifetime. HZ affecting the first division of the trigeminal nerve (**HZ ophthalmicus**) is the second most common form of HZ, second only to the involvement of the thoracic dermatomes and comprises 10% to 20% of all HZ cases. The second and third divisions of the trigeminal nerve are rarely if ever affected in isolation. HZ begins with a prodrome that includes fatigue and malaise, headache and photophobia, rarely fever but very frequently includes a vague sensory prodrome in the involved dermatome that consists of tingling paresthesias, sometimes burning paresthesias, sometimes lancinating paresthesias, and sometimes allodynia. The HZ induced paresthesias are sensed as surface, dermatomal phenomena but a perceived deeper discomfort described as muscle or bone ache or even visceral pain referred to as myotomal phenomena in the older literature also occurs and can be severe. After a period of about 1 to 5 days, the typical rash (shingles), first maculopapular, and then frankly vesicular appears, restricted to a primary dermatome and parts of the immediately contiguous dermatomes. As the rash advances, the pain may worsen, and pruritus develops. The pain is mixed and unrelenting; a lancinating component may be prominent but never singular. A patient's scratching will alter the appearance of the rash, with excoriations obscuring vesicles and it is therefore important to remain watchful for secondary bacterial infection. Bilateral or multifocal involvement is seen only in the immune compromised. Rarely, patients perceive a prodrome including sensory symptoms without evidence of rash. (This phenomenon together with the sequelae of HZ in the absence of observed rash have been termed "zoster sine herpete.") The rash generally subsides over a period of 30 days; pain generally declines with it, but in 10% to 20% of patients, the pain persists beyond 30 days. This persistent pain syndrome termed postherpetic neuralgia (PHN) is the most common complication of HZ.

It is important to remember that HZ ophthalmicus often brings with it ocular involvement that can include exposure keratitis and uveitis but may rarely include retinal vasculitis, ischemic optic neuropathy, or necrotizing retinopathy. For these reasons, one should involve an ophthalmologist early in the course of illness, and treat the patient aggressively. The initiation of oral antiviral therapy within 72 hours of the appearance of rash reduces both the duration and severity of an outbreak while delayed treatment may still be beneficial. Intravenous antiviral therapy for the immune incompetent or for severe cases must be considered. Topical antiviral and either systemic or topical corticosteroid may be employed in selected cases.

Although generally self-limited, PHN may last many months or even years. PHN becomes more common in the elderly, and probably more debilitating and more difficult to treat in the older old. Manifestations include burning, lancinating or aching pain hyperalgesia, and allodynia. Allodynia is prominent and together with other neuropathic pain may severely disturb daily social function. The persistence of pain reflects CNS changes

("central pain") and possibly persistent low-grade viral activity. Treatment is patient specific. Both gabapentin and pregabalin are Food and Drug Administration (FDA) approved for the treatment of PHN. A combination of opioid analgesics and AEDs can be used. Tricyclic antidepressants may also be effective. The application of topical sodium channel-directed analgesics such as lidocaine as an ointment or in patch form can be effective and topical capsaicin may be effective. The use of intrathecal corticosteroid is controversial.

The practitioner should be aware of rare but potentially devastating sequelae of HZ including cranial polyneuritis, CNS vasculitis, cerebral infarction, cerebral hemorrhage, postinfectious myelitis, progressive myelopathy, and necrotizing retinopathy. Childhood vaccination against HZ became available in 1995 and may alter the epidemiology of this disorder over time, but in the interim a much higher dose attenuated live virus vaccine approved by the FDA is available to people over age 60. As demonstrated by the initial trial and subsequently confirmed, the vaccine reduces the incidence of HZ by one-half. PHN is reduced by two-thirds.

IV. PRIMARY HEADACHE DISORDERS

Primary headaches, migraine, and its relatives can present with facial pain as a primary or principle feature. Chronic migraineurs, especially those without aura, will not infrequently attribute their problem incorrectly to recurrent sinus infection with infraorbital or retro-orbital pain. In the absence of signs and symptoms of infection and in the absence of unequivocal imaging support, a wary practitioner should consider the diagnosis of chronic migraine or chronic daily headache, even with tension type characteristics. A careful history of the patient's pain complaint including quality, location, timing, duration, frequency, triggers, associated symptoms, and pattern of drug use or overuse should guide the clinician toward a correct diagnosis and best treatment. Headache of more than 1 hour's duration, pain that is often but not always unilateral, the presence of photophobia, phonophobia, and a reluctance to move, anorexia if not frank nausea with vomiting, the presence of recurrent aura such as bright scotoma or transient hemianopsia or hemifacial or hemibody numbness or the presence of typical triggers such as bright lights, strong odors, noisy environments, or alcohol should influence the practitioner toward a consideration of migraine as a possible diagnosis. The localization of pain in migraine patients is variable, and although infrequent, it is not unusual for patients to report pain mostly involving the face or even entirely limited to the lower face.

Cluster headache (CH), the less common paroxysmal hemicranial headache and the very rare related headache variant, short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing or short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) syndrome can pose initial diagnostic uncertainty. These three pain syndromes are grouped collectively as the TACs. The pain of CH is always severe, usually peri- and retro-orbital, unilateral, and relatively short lasting. The pain is described as stabbing or knife-like, boring or drilling, burning or squeezing and in some patients may spread to the occiput and posterior cervical regions. Attack duration is typically from 15 minutes to 3 hours but most attacks last less than 1 hour. During the attack, the patient appears restless and agitated, a feature which effectively differentiates this form of headache from migraine. The attacks are cyclical, tend to occur at characteristic times of the day, and occur on a once up to several times daily basis for weeks or months and then spontaneously resolve. It is the cyclical grouping from which the term "cluster" originates. The most severe headaches are said to wake the patient from sleep early in the night, corresponding to the first rapid eye movement sleep cycle. The attacks are accompanied by a combination of lacrimation, conjunctival injection, nasal congestion, or rhinorrhea. Sometimes Horner syndrome can be observed. These autonomic manifestations are generally unilateral. Affected individuals are more commonly men and smokers. Recent data suggest lifetime prevalence could be as high as 1 in 1,000. Cluster pain is severe, suicidal ideation during attacks is not unusual, and aggressive treatment is mandatory. Multiple abortive therapies can be effective. Rapidly absorbed tryptans works; both sumatriptan and zolmitriptan are believed to be effective. High-flow inhaled nasal oxygen can also be an effective abortive therapy.

Many different treatments are used by specialty clinics. Transitional and prophylactic therapies are often indicated. Treatment usually requires polypharmacy and ongoing therapy is probably best delivered by a practitioner familiar with the problem. Specialty clinic estimates suggest that 10% of chronic CH patients are resistant to or intolerant of all pharmacotherapy. Interventional therapy such as occipital nerve stimulation or hypothalamic deep brain stimulation may work but efficacy is uncertain and consideration of these therapies should be limited to very experienced centers. Although CH is distinctly clinically recognizable, MRI of the brain with special reference to the skull base is advisable on initial presentation.

Paroxysmal hemicrania consists of multiple severe short lasting bouts of pain, lasting only minutes, with a pain distribution which is unilateral, often orbital or supraorbital, retroorbital or temporal. In SUNCT, the pain is even briefer, lasting seconds. The character of the pain in SUNCT and to a lesser degree in paroxysmal hemichrania make it difficult to distinguish these clinically from the pain of neuralgia but both syndromes are accompanied by cranial autonomic features that should distinguish them from TN. Paroxysmal hemicrania responds nearly always to indomethacin as does another headache syndrome with even briefer lasting painful jolts, primary stabbing headache. The extraordinarily rare SUNCT syndrome may respond to lamotrigine or one of the other newer AEDs. In rare patients, headache classifiable as SUNCT may represent a crossover form of TN and could respond to surgical therapy.

It must be remembered that primary headache including migraine and its variants remains a diagnosis of exclusion. Appropriate neuroimaging must be considered at initial presentation or if the clinical characteristics of the syndrome shift significantly.

V. PERSISTENT IDIOPATHIC FACIAL PAIN OR ATYPICAL FACIAL PAIN

Atypical facial pain arose historically as a diagnostic grouping in contradistinction to TN (or "typical" facial pain) and has recently been renamed PIPF by the International Headache Society who have generated a defining set of characteristics. These are chronicity, dull constant aching (or burning) pain with nonperiodic exacerbations, diffusely localized pain usually unilateral but not conforming to a nerve distribution, a normal neurologic examination, and pain without an attributable cause after adequate clinical and imaging investigation. PIFP patients are less commonly young and less commonly male, are frequently depressed and frequently have other accompanying somatic complaints. These patients too often come to neurologic attention after one or more interventions, often dental or sinus procedures that have failed to alleviate and may have even aggravated their complaint. A multidisciplinary approach to these patients is advocated and antidepressants are frequently helpful. Amitriptyline is an established therapy but selective norepinephrine and serotonin reuptake inhibitors such as duloxetine may be helpful. Unfortunately, therapy is rarely dramatically successful in patients with PIFP. For patients where the duration of the complaint is a many years long, it is important to obtain a history of the earliest presenting features. Some of these patients may have a chronically evolved form of TN. When the complaint is relatively new one, a rare patient may actually have an underlying pulmonary malignancy. These patients will be heavy smokers and generally have a prominent periauricular component to their pain syndrome.

VI. LOWER FACIAL AND ORAL PAIN

Both the general practitioner and the neurologist should be familiar with pain disorders involving the lower face. The most common of these are the temporomandibular disorders (TMJ syndromes). Although temporomandibular dysfunction presents principally with pain at the TMJ and its associated musculature, associated symptoms including ear pain, frontal facial pain, more generalized headache, cervical pain, and dizziness make TMJ disorders an important differential consideration in patients presenting with facial pain. Historically, the

TMJ dysfunctions have been both overdiagnosed and overtreated. TMJ syndromes present principally with pain involving the TMJ and its associated musculature, aggravated by jaw function and associated with asymmetric movements of the jaw, painfully limited jaw opening and joint sounds. TMJ dysfunction presents most frequently in young adults, with a gender disparity favoring women in ratios of 3:1 or more. These disorders are generally self-limiting, and rarely present or persist beyond the age of 40. It is estimated that only 5% of symptomatic patients require any therapy at all, and it is believed that contrary to some historical practices, very few patients require invasive diagnostics or invasive therapies. The vast majority of patients with TMJ syndromes will respond to anti-inflammatory medications and conservative measures such as jaw appliances. The majority of patients refractory to these simple measures have a chronic pain syndrome and should be considered for multidisciplinary therapy, which may include benzodiazepines and norepinephrine reuptake inhibitors. Narcotic analgesics should be avoided. Physical findings in TMJ dysfunction include tenderness of the TMJ and associated musculature and painful, limited or asymmetric jaw opening. Evaluation by an appropriate dental or oral surgical practitioner is recommended.

Atypical odontalgia is a rare disorder that mimics common tooth pain. The syndrome is characterized by its chronic nature, by definition more than 4 months duration and is frequently seen following dental extraction (phantom tooth pain), other oral procedures, or oral trauma. On occasion, the syndrome appears to occur spontaneously. The pain is characterized by dull persistence but transient sharp pain is sometimes reported. This pain entity is said not to disturb sleep and may not be present at awakening or briefly thereafter. Hyperpathia and allodynia may be present while spread of the pain to contiguous structures is not uncommon. Once local pathology has been adequately excluded, typical treatments targeting neuropathic pain may prove helpful.

VII. OTHER CAUSES OF FACIAL PAIN

The signs and symptoms of acute infections of the oral cavity, the paranasal sinuses, or the eye are generally obvious. The practitioner must remain alert to the patient who has been treated surreptitiously and unsuccessfully for a poorly documented acute infection where an alternative diagnosis, inflammatory or neurologic, should be considered. Chronic sinusitis, especially when the deep sinuses are involved, can be clinically less apparent and could present with only vague head or facial pressure and malaise. Modern imaging, either coronal CT or when needed MRI, is highly sensitive to pathology in or neighboring the ethmoid or sphenoid sinuses. The possibility of chronic facial pain heralding the presence of invasive infection in diabetics or the immune compromised must not be overlooked.

Giant cell arteritis should be considered in patients above age 55 who present subacutely with temporal or facial pain coupled with marked fatigue and malaise. These patients may complain of scalp tenderness, jaw claudication on prolonged chewing, and most ominously, visual disturbance. Palpable tenderness of the superficial temporal artery or another branch of the extracranial carotid artery should be present on examination and an elevated erythrocyte sedimentation rate will be present in nearly 90% of cases. A timely temporal artery biopsy is essential to making the correct diagnosis.

Cranial neuropathies can present with pain prior to the development of neurologic deficits. Retrobulbar neuritis very frequently presents with pain on eye movement before monocular visual loss becomes apparent. Ischemic neuropathies involving the third or the sixth cranial nerves are typically painful although nonarteritic ischemic optic neuropathy is not.

Cervical arterial dissection can present with retro-orbital or more diffuse facial or occipital pain. Cervical pain need not be present and Horner syndrome can be either absent or overlooked. Pain frequently precedes cerebral ischemic manifestations so this entity is important to consider in young adults, especially if there is a recent history of minor head or neck trauma or cervical manipulation.

Acute glaucoma is associated with orbital and adjacent facial pain but the diagnosis is usually obvious because of corneal clouding and other eye changes. Subacute glaucoma can be more subtle on physical examination and can lead to a late or missed diagnosis. Facial pain or headache should not be readily attributed to refractive errors or eye strain.

Chronic facial pain accompanied by hyperpathia or allodynia can be a manifestation of a central pain syndrome. The most common of these involves the contralateral thalamus and is usually post ischemic. Generally, complete hemisensory loss will be present but on occasion, the loss can be restricted to the trigeminal distribution alone. This form of central pain may readily respond to tricyclic antidepressants such as amitriptyline or to antiepileptic medications such as lamotrigine or gabapentin.

Anesthesia dolorosa is a central pain syndrome that may follow any of the procedures performed to control TN. It is thought to be a consequence of excessive deafferentation and is characterized by the simultaneous presence of a constant, very unpleasant dysesthesia, and marked cutaneous facial sensory loss. The syndrome may not surface for weeks or months after an ablative procedure. Neurosurgeons have observed that lessening the degree of deafferentation can lessen the likelihood of anesthesia dolorosa following an ablative trigeminal procedure. This syndrome can be difficult to treat either medically or surgically. Experimental approaches utilizing either invasive or noninvasive brain stimulation technologies could prove effective in the near future.

VIII. CONCLUDING OBSERVATIONS

It should always be remembered that patients with a chronic complaint, even if that complaint has been thoroughly investigated, can develop new symptoms and become refractory to previously effective therapy. Changes in complaint or condition in an otherwise familiar patient could reflect a serious underlying pathology and may merit repeat neuroimaging. Patients with chronic facial pain may harbor an undisclosed malignancy or inflammatory process or a chronic infectious process. The presence of neurologic deficits on examination, be it a cranial nerve palsy, a sensory deficit in the trigeminal distribution, Horner syndrome or the presence of subjective complaints of dysesthesias, diplopia, hearing loss, or disequilibrium should alert the practitioner to these possibilities. Similarly, the presence of cervical lymphadenopathy, chronic nasal obstruction, proptosis, lid edema, serous otitis, or an objective bruit is potentially grave signs.

Patients with deficits should be appropriately imaged and referred. If patients with TN do not immediately respond to medication, they should be seen by a neurologist or neurosurgeon. If patients with TN fail medical therapy, consideration of early invasive treatment is generally appropriate. Because of its rarity, the diagnosis of GN should be confirmed by a neurologist or neurosurgeon. Patients with unusual headache syndromes should have their diagnosis confirmed by a neurologist and if management difficulties are encountered, managed by a neurologist with headache expertise. Patients with HZ ophthalmicus should be seen by an ophthalmologist even if the globe appears uninvolved. Patients with refractory PHN can be expected to do poorly following ablative therapy.

Patients with chronic facial pain would truly benefit from a medical home provided by either their primary care physician or an appropriate specialist, perhaps a neurologist, who can propose new avenues of investigation or therapy and help prevent inappropriate interventions.

Recommended Readings

Evans RW, Agostoni E. Persistent idiopathic facial pain. *Headache*. 2006;46(8):1298–1300.

Gronseth G, Cruccu G, Alksne J, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. *Neurology*. 2008;71(15):1183–1190.

Leone M, Bussone G. Pathophysiology of trigeminal autonomic cephalalgias. *Lancet Neurol.* 2009;8(8):755–764.

Obermann M. Treatment options in trigeminal neuralgia. *Ther Adv Neurol Disord*. 2010;3:107.

Sorivani SJ, Keith DA, Kaban LB. Temporomandibular disorders. *N Eng J Med.* 2008;359:2693–2705.

Tatli M, Satici O, Kanpolat Y, et al. Various surgical modalities for trigeminal neuralgia: literature study of respective long-term outcomes. *Acta Neurochir (Wien)*. 2008;150(5):243–255.

Tseng, HF, Smith N, Harpaz R, et al. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. *JAMA.* 2011;305(2):160–166.

CHAPTER

15 Approach to the Patient with Facial Weakness

John Leonetti and Sam J. Marzo

All human emotions and expressions are conveyed via the complex interactions of facial muscle groups innervated by the **seventh cranial nerve (CN VII).** Facial weakness or paralysis can, therefore, lead to both physical and psychological distress. The deficits are both cosmetic and functional. A logical assessment algorithm must be utilized in order to implement timely and effective diagnostic studies and treatment protocols.

I. ANATOMY

A. Central pathway. The somatomotor cortex in the precentral gyrus provides facial nerve projection fibers, and the cell bodies in this area are primarily pyramidal nerve cells. Fascicles of the **corticobulbar** tract project through the internal capsule, through the basal part of the pons within the pyramidal tracts. Most of the nerve fibers decussate to reach the facial nucleus on the opposite side. Some fibers innervate the ipsilateral facial nucleus accounting for emotional control of facial expression.

The **facial motor nucleus** (7,000 neurons) is within the reticular formation beneath the fourth ventricle. The superior (ventral) facial nucleus receives bilateral cortical input, whereas the inferior (dorsal) portion of the facial nucleus receives only contralateral cortical input for lower facial musculature innervation; hence, the "**forehead sparing**" clinical finding in patients with a unilateral cortical (upper motor) versus a peripheral (lower motor) lesion.

In addition to the motor fibers of the facial nerve responsible for facial expression, there are sensory fibers for taste to the anterior two-thirds of the tongue **(chorda tympanii)**, external auditory canal cutaneous sensation, along with parasympathetic fibers to the lacrimal, submandibular, and sublingual glands.

The facial nerve enters the internal auditory canal with the cochleo-vestibular nerve (CN VIII) and the nervus intermedius after leaving the pons and traversing the cerebellopontine angle.

B. Transtemporal. The facial nerve is located in the antero-superior portion of the internal auditory canal. Upon entering its own fallopian canal, the dural covering is replaced with epineurium. The three intratemporal segments of the facial nerve are the labyrinthine, tympanic, and mastoid segments. The facial nerve exits the skull at the stylomastoid foramen.

C. Extratemporal. The facial nerve exits the stylomastoid foramen and divides into the upper (temporofacial) and lower (cervicofacial) segments. A variety of anastomotic branching occurs between the commonly identified temporal, zygomatic, buccal, mandibular, and cervical branches of the facial nerve.

II. CLINICAL ASSESSMENT

A. History. The single most important information obtained in the clinical history of a patient with facial paralysis is the rate of onset of the facial weakness. Acute onset of facial weakness, if nontraumatic, may be vascular or viral in origin. Subacute onset of facial

weakness is usually idiopathic **(Bell's palsy)**, whereas delayed, gradual, and progressive facial weakness may be caused by intracranial, intratemporal, or extracranial neoplasms.

Other important factors in the history of facial weakness include whether the deficit is unilateral or bilateral, any past history of similar facial weakness, a history of ipsilateral hearing loss, associated ear or facial pain, trismus, or temporal trauma.

A general medical history can also assist in the evaluation of facial weakness. Predisposing factors include patient's age, hypertension, diabetes mellitus, cigarette smoking, and a prior history of facial weakness. Lyme's disease, Sjogren's syndrome, and a history of facial skin cancer may also be associated with facial paralysis.

B. Physical examination. Upper motor neuron (UMN) facial weakness caused by a contralateral brainstem lesion above the level of the upper medulla oblongata affects only the lower facial muscles. The forehead movement and eye closure are normal. The corneal reflex and emotional facial movements are intact.

Lower motor neuron (LMN) lesions from the facial nucleus to the parotid gland cause weakness of all branches of the facial nerve. Complete paralysis is apparent with voluntary and emotional (involuntary) attempts to animate the face, and the corneal reflex is impaired (Table 15.1—House-Brackmann Scale).

TABLE 15.1 House-Brackmann Classification of Facial Function

Grade	Characteristics
I, normal	Normal facial function
II, mild dysfunction	*Gross* Slight weakness noticeable on close inspection May have slight synkinesis At rest, normal symmetry and tone *Motion* Forehead—moderate to good Eye—complete closure Mouth—slight asymmetry
III, moderate dysfunction	*Gross* Obvious, not disfiguring Noticeable synkinesis, contracture, spasm At rest, normal symmetry and tone *Motion* Forehead—slight to moderate movement Eye—complete closure with effort Mouth—slightly weak with maximal effort
IV, moderately severe dysfunction	*Gross* Obvious weakness and/or disfiguring asymmetry At rest, normal symmetry and tone *Motion* Forehead—none Eye—incomplete closure Mouth—asymmetric with maximum effort
V, severe dysfunction	*Gross* Barely perceptible motion At rest, asymmetry *Motion* Forehead—none Eye—incomplete closure Mouth—slight movement
VI, total paralysis	No movement

A complete neurologic examination may identify other focal findings such as other cranial nerve deficits, hemiparesis, hemisensory loss, sensorineural hearing loss (SNHL), or gaze palsy. Facial skin inspection may demonstrate a malignant lesion causing perineural invasion and facial weakness, whereas bimanual parotid palpation, especially in the patient with trismus, can identify a parotid gland malignancy as a cause for facial paralysis. Microscopic otoscopy will help disclose an infectious (acute otitis media) or neoplastic source of facial weakness within the middle ear of mastoid bone.

C. Diagnostic studies.

1. **CT** of the temporal bones is useful in patients with acute otitis media, temporal bone fractures, or suspected primary temporal bone tumors (facial neuroma, glomus tumor, and minor salivary gland neoplasm).
2. **MRI** with contrast is useful in patients with suspected brainstem, cerebellopontine angle, or parotid gland lesions.
3. **Lumbar puncture** is utilized in cases of suspected meningitis, vasculitis, or meningeal carcinomatosis.
4. **Electrodiagnostic studies** such as electroneuronography may be used to follow or grade the subclinical recovery of the facial nerve. These studies, like the tear and salivation tests, add little to the ability to diagnose the cause of facial paralysis.
5. **Audiometric testing** will help determine the type and degree of hearing loss. An asymmetric, ipsilateral SNHL would suggest a cerebellopontine angle or internal auditory canal lesion in patients with LMN facial weakness. A conductive or mixed hearing loss, however, would suggest a middle ear infectious or neoplastic cause for the facial nerve deficit.

III. DIFFERENTIAL DIAGNOSIS

The most common cause of facial paralysis is **Bell's palsy**. It is a diagnosis of exclusion. The paralysis can be partial or complete, is unilateral, and occurs suddenly over 24 to 48 hours.

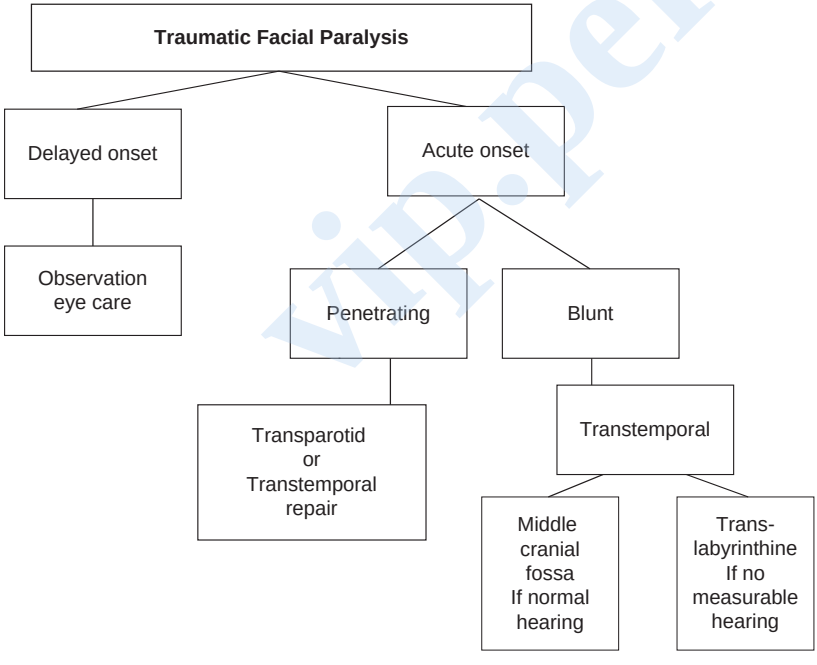


FIGURE 15.1 Clinical assessment algorithm for patients with traumatic facial paralysis.

It is currently believed to be secondary to a herpetic inflammation of the nerve. Approximately 70% of patients recover completely without treatment.

Oral steroids and antiviral therapy, when given within the first 10-14 days after onset, may have a role in improving the ultimate patient outcome. However, recent data show that antivirals do not provide an added benefit on facial recovery.

Ramsay Hunt's syndrome is characterized by aural vesicles, pain, and facial palsy. The vesicles can also involve the ipsilateral anterior two-thirds of the tongue and soft palate. It differs from Bell's palsy in that vesicles are present, pain may be severe and persistant, there is a higher incidence of vestibular and auditory symptoms, and the prognosis is generally worse. The agent is believed to be **varicella-zoster virus.** Oral steroids and antiviral therapy are the currently accepted treatment.

Melkersson–Rosenthal's syndrome is characterized by recurring facial paralysis. The paralysis may be unilateral or may alternate sides, and may be complete or incomplete. It can occur in males or females, usually in the second decade of life. Associated physical features also include edema of the eyelids, as well as fissuring of the tongue.

Traumatic causes for facial paralysis can be penetrating or blunt. **Penetrating injury** to the extratemporal, intraparotid facial nerve can be microsurgically repaired if the wound is clean, if performed as soon as feasibly possible, and if the injury involves the main trunk or a primary division of the facial nerve. Individual branch lacerations do not require surgical repair. Penetrating injury to the facial nerve within the temporal bone also requires surgical repair and, if necessary, interposition grafting with the greater auricular nerve.

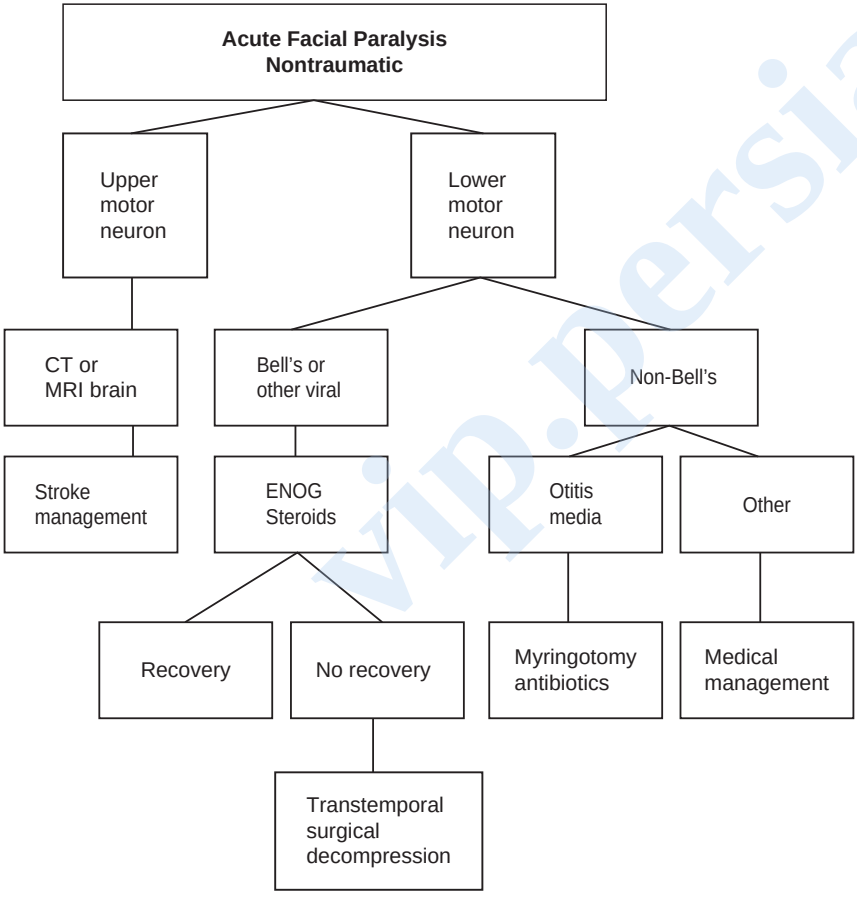


FIGURE 15.2 Clinical assessment algorithm for patients with acute, nontraumatic facial paralysis.

Blunt trauma to the temporal bone may cause facial paralysis as a result of neural contusion, hematoma, edema, bony impingement, laceration, or avulsion. Delayed onset facial weakness is usually due to compression with neural edema. These patients generally recover excellent facial function without surgical or medical intervention. Acute-onset facial weakness following blunt temporal bone trauma, however, suggests more serious neural injury requiring transmastoid facial nerve decompression and repair (Fig. 15.1).

Congenital facial paralysis can be related to intrauterine or delivery-related trauma, facial nucleus aplasia, facial musculature aplasia, or be associated with more complex general syndromes. **Cardiofacial syndrome** consists of unilateral facial palsy with congenital heart defects. **Poland's** and **Goldenhaar's syndromes** may occasionally be associated with facial weakness. Bilateral facial palsy with abducens nerve palsy occurs in **Möbius syndrome**. **Myotonic dystrophy** is a subclassification of muscular dystrophy, which can be associated with facial palsy and medical disorders, such as hypertension, can be related to the onset of facial weakness.

Nontraumatic acute facial paralysis due to a stroke, brain tumor, or brain abscess can manifest as an UMN weakness, whereas Bell's palsy, acute otitis media, Ramsay–Hunt's syndrome (herpes zoster oticus), and iatrogenic injury following otologic or parotid surgery result in complete, unilateral LMN paralysis (Fig. 15.2).

Nontraumatic, delayed facial paralysis is usually due to a neoplasm (Fig. 15.3). If the patient complains of associated hearing loss and tinnitus, the lesion is likely to be found in the cerebellopontine angle or the internal auditory canal. Slow-growing facial neuromas and glomus tumors may cause a mixed hearing loss if the tumor is isolated to

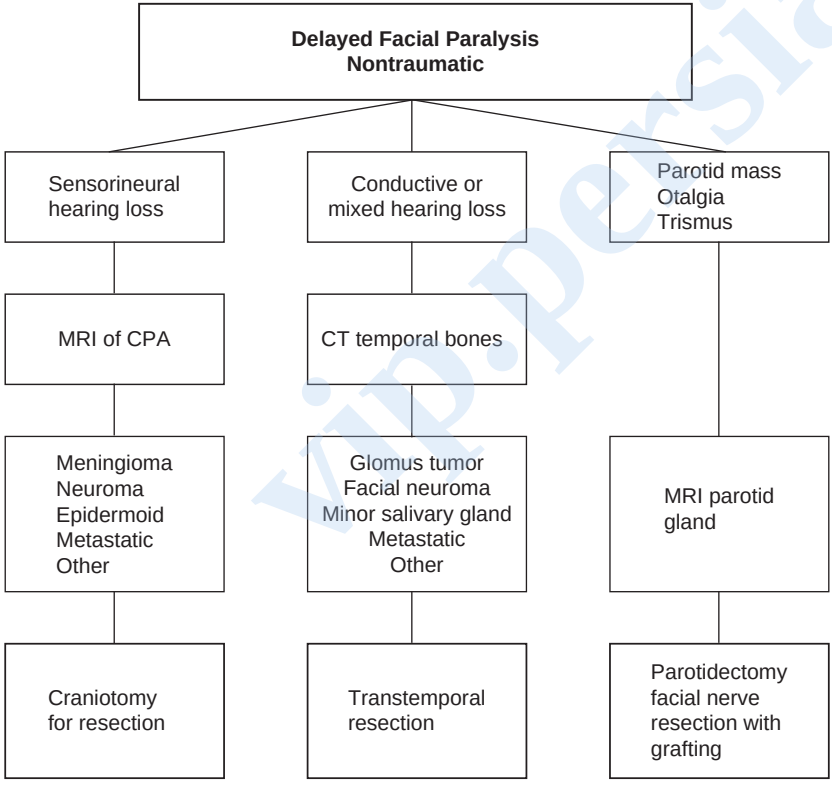


FIGURE 15.3 Clinical assessment algorithm for patients with delayed, nontraumatic facial paralysis.

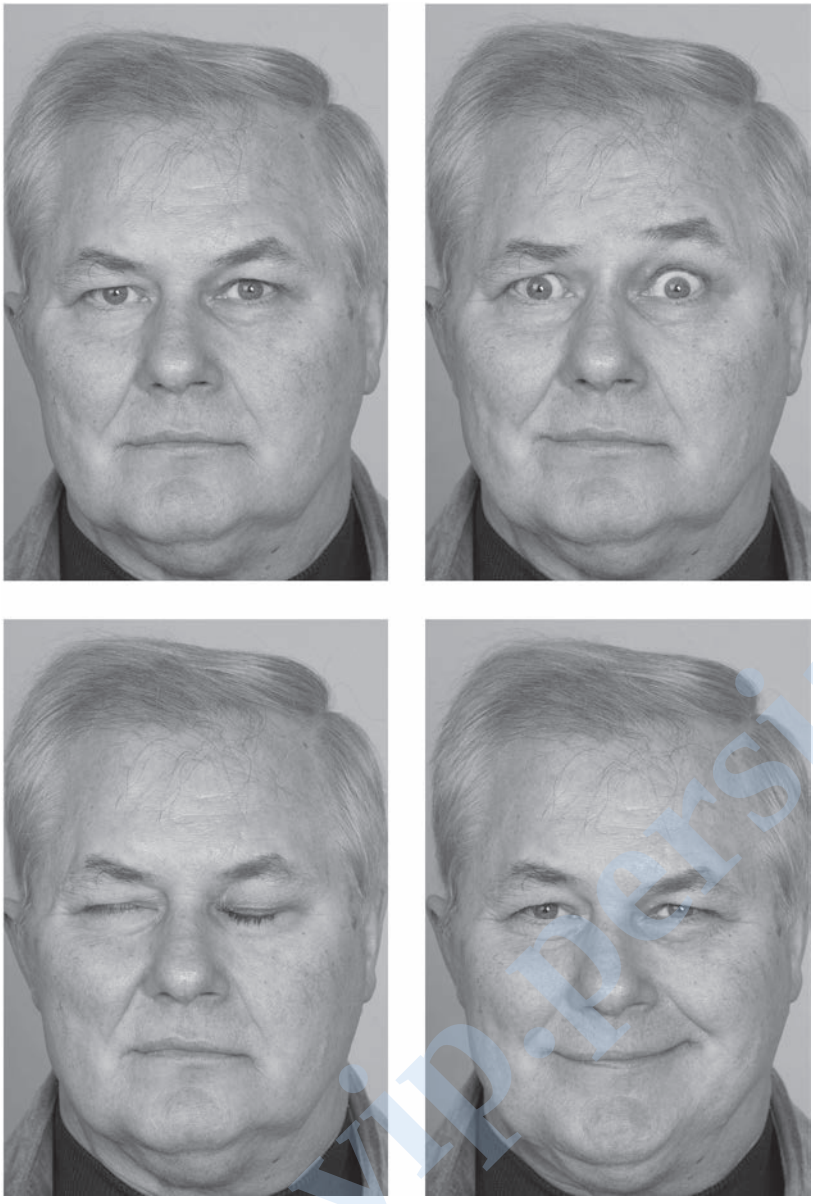


FIGURE 15.4 Long-term facial function following parotidectomy, facial nerve resection, and interposition neural grafting for acinic cell carcinoma of the parotid gland.

the middle ear and/or mastoid bone. Malignant parotid tumors also cause gradual onset or segmental facial paralysis in addition to otalgia, facial pain, trismus, and bloody otorrhea (Fig. 15.4). Benign parotid tumors, other than intraparotid facial neuromas, rarely cause facial paralysis.

A more inclusive list of causes for facial paralysis is included in Table 15.2.

TABLE 15.2 Causes of Facial Paralysis

Birth	Molding Forceps delivery Myotonic dystrophy Möbius syndrome (facial diplegia associated with other cranial nerve deficits)
Trauma	Basal skull fractures Facial injuries Penetrating injury to middle ear Altitude paralysis (barotrauma) Lightning
Neurologic	Opercular syndrome (cortical lesion in facial motor area) Millard–Gubler's syndrome (abducens palsy with contralateral hemiplegia caused by lesion in vertical pons involving the homolateral CN VII nucleus and the descending corticospinal tract)
Infection	External otitis Otitis media Mastoiditis Chickenpox Herpes zoster cephalicus (Ramsay–Hunt's syndrome) Encephalitis Poliomyelitis (Type 1) Mumps Mononucleosis Leprosy Influenza Coxsackievirus Malaria Syphillis Scleroma Tuberculosis Botulism Acute hemorrhagic conjunctivitis (enterovirus 70) Gnathostomiasis Mucomycosis Lyme's disease Cat scratch AIDS
Metabolic	Diabetes mellitus Hyperthyroidism Pregnancy Hypertension Acute porphyria Vitamin A deficiency
Neoplastic	Benign lesions of parotid Cholesteatoma Seventh nerve tumor Glomus jugulare tumor Leukemia Meningioma Hemangioblastoma Sarcoma Carcinoma (invading or metastatic) Anomalous sigmoid sinus

TABLE 15.2 Causes of Facial Paralysis (Continued)

	Carotid artery aneurysm Hemangioma of tympanum Hydradenoma (external canal) Facial nerve tumor (cylindroma) Schwannoma Teratoma Hand-Shüller-Christian disease Fibrous dysplasia Neurofibromatosis Type 2
Toxic	Thalidomide (Miehlke syndrome, cranial nerves VI and VII with congenital malformed external ears and deafness) Ethylene glycol Alcoholism Arsenic intoxication Tetanus Diphtheria Carbon monoxide
Iatrogenic	Mandibular block anesthesia Antitetanus serum Vaccine treatment for rabies Postimmunization Parotid surgery Mastoid surgery Post-tonsillectomy and adenoidectomy Iontophoresis (local anesthesia) Embolization Dental
Idiopathic	Familial Bell's palsy Melkersson-Rosenthal syndrome (recurrent alternating facial palsy, furrowed tongue and faciolabial edema) Hereditary hypertrophic neuropathies (Charcot-Marie Tooth disease Dejerine-Sottas disease) Autoimmune syndrome Amyloidosis Temporal arteritis Thrombotic thrombocytopenic purpura Polyateritis nodosa Guillain-Barré syndrome (GBS) Multiple sclerosis Myasthenia gravis Sarcoidosis Osteopetrosis

Adapted from May M, Klein SR. Differential diagnosis of facial nerve palsy. *Otolaryngol Clin North Am*. 1991;24(3):613–145, with permission.

Recommended Readings

Adour KK. Diagnosis and management of facial paralysis. *N Engl J Med.* 1982;307:348–351.
Bateman DE. Facial palsy. *Br J Hosp Med.* 1992;47:430–431.
Carpenter B, Sutin J. *Pons in Human Neural Anatomy*. Baltimore, MD: Williams and Wilkins; 1983:385–389.
Courbille J. The nucleus of the facial nerve. The relation between cellular groups and peripheral branches of the nerve. *Brain.* 1966;1:338–354.

Esslen E. Electromyography and electroneurography. In Fisch U, ed. *Facial Nerve Surgery*. Birmingham, UK: Aesculapius; 1977:93–100.

Engström M, Berg T, Stjernquist-Desatnik A, et al. Prednisolone and valaciclovir in Bell's palsy: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet Neurol. 2008; 7(11) 993-1000.

Finestone AJ, Byers K. Acute facial paralysis: is it a stroke or something else? *Geriatrics*. 1994;49:50–52.

Fisch U, Esslen E. Total intratemporal exposure of the facial nerve: pathologic findings in Bell's palsy. *Arch Otolaryngol*. 1972;85:335–341.

Gupta MK, Kumar P. Reversible congenital facial nerve palsy: an uncommon cause of asymmetric crying facies in the newborn. *Internet J Pediatr Neonatol*. 2007, Volume 7, Number 1. ISSN 1528-8374.

House JW, Brackman DE. Facial nerve grading system. *Otolaryngol Head Neck Surg*. 1985;93:146–147.

Morgan M, Nathwani D. Facial palsy and infections: the unfolding story. *Clin Infect Dis*. 1992;14:263–271.

Nager GT, Proctor B. Anatomical variation and anomalies involving the facial canal. *Ann Otol Rhinol Laryngol*. 1982;(suppl 93):45–61.

Olsen KD. Facial nerve paralysis: all that palsies is not Bell's. *Postgrad Med*. 1984;76:95–105.

Quant EC, Jeste SS, Muni RH, et al. The benefits of steroids plus antivirals for treatment of Bell's palsy: a meta-analysis. BMJ. 2009; 339:b3354.

Pietersen E. Natural history of Bell's palsy. *Acta Otolaryngol*. 1992;492(suppl):122–124.

Smith JD, Crumley RL, Harker A. Facial paralysis in the newborn. *Arch Otolaryngol Head Neck Surg*. 1981;89: 1021–1024.

Sunderland S. *Nerve and Nerve Injuries*. 2nd ed. Edinburgh, UK: Churchill Livingstone; 1978:31–60.

Terao S, Miura N, Takeda A, et al. Course and distribution of facial corticobulbar tract fibers in the lower brain stem. *J Neurol Neurosurg Psychiatry*. 2000;69:262–265.

Toelle SP, Boltshauser E. Long-term outcome in children with congenital unilateral facial nerve palsy. *Neuropediatrics*. 2001;32:130–135.

Wackym PA. Molecular temporal bone pathology II. Ramsay Hunt syndrome (herpes zoster oticus). *Laryngoscope*. 1979;107:1165–1175.

CHAPTER

16 Approach to the Patient with Dizziness and Vertigo

Timothy C. Hain

Dizziness and vertigo are common symptoms. About 2.5% of all primary care visits are for dizziness and about 1% are for vertigo. Dizziness and vertigo have diverse etiologies. Thus, a broadly based approach to the dizzy patient is necessary, at times requiring serious and life-threatening medical problems such as cardiac arrhythmia to be distinguished from the more common inner ear diseases and dizziness from unlocalizable sources.

I. ETIOLOGY

Vertigo can be categorized into four types: otologic, central, medical, and unlocalized (Table 16.1).

A. Otologic vertigo is caused by dysfunction of the inner ear. It accounts for about one-third of all patients with vertigo. Table 16.1 lists entities that account for about 95% of all cases of otologic vertigo. The distribution of diagnoses varies greatly according to the referral base (e.g., neurology, otolaryngology, general medicine, and emergency room), but in all settings otologic vertigo comprises a substantial component.

1. **Benign paroxysmal positional vertigo (BPPV)** is the most common single type of otologic vertigo, accounting for roughly 20% of vertigo of all causes and 50% of all otologic cases. BPPV presents with brief vertigo provoked by changes in the orientation of the head to gravity. BPPV is caused by loose debris within the labyrinth.
2. **Vestibular neuritis** presents with vertigo, nausea, ataxia, and nystagmus. It is attributed to a viral infection of the vestibular nerve. Labyrinthitis presents with the same symptom complex, combined with tinnitus and/or hearing loss. Vestibular neuritis and labyrinthitis together account for about 15% of all otologic vertigo cases.
3. **Ménière's disease** presents with intermittent vertigo accompanied by hearing complaints (see the so-called "hydrops" symptom complex in IV.A.3). It accounts for about 15% of otologic vertigo cases.
4. **Bilateral vestibular paresis** presents with oscillopsia and ataxia, usually caused by loss of vestibular hair cells. The typical history is of treatment for several weeks with an intravenous or intraperitoneal ototoxic antibiotic (of which gentamicin is the most commonly used). Bilateral vestibular loss is uncommon.
5. **The superior canal dehiscence (SCD) syndrome** exemplifies several conditions in which there is an opening between the inner ear and a surrounding structure. They generally present with vertigo induced by sound (the Tullio's phenomenon) or as ataxia provoked by activity or straining. The diagnosis of SCD has been rapidly increasing in recent years due to a combination of improved knowledge about the condition as well as greater use of a new diagnostic modality—vestibular evoked myogenic potentials (VEMP). In SCD, bone over the superior semicircular canal is absent. Similar symptoms are seen in perilymphatic fistula and cholesteatoma.
6. **Tumors compressing the eighth cranial nerve, such as acoustic neuroma,** present with asymmetric hearing loss combined with mild ataxia. Eighth nerve tumors are very uncommon in the vertiginous population (but are more common in the unilaterally hearing impaired).

B. Central vertigo is caused by dysfunction of central structures that process sensory input from the inner ear. Central vertigo accounts for 2% to 50% of vertigo diagnoses, depending on the setting in which patients are seen. In a majority of cases, central vertigo is caused by migraine. Table 16.1 lists entities accounting for about 90% of central

TABLE 16.1 Etiologies of Vertigo

Otologic vertigo
BPPV
Vestibular neuritis and labyrinthitis
Ménière's disease
Bilateral vestibular paresis or loss
Superior Canal Dehiscence (SCD) and Perilymph Fistula (PLF)
Tumors compressing the eighth cranial nerve
Central vertigo
Migraine
Stroke and TIA in vertebrobasilar arterial distribution
Seizures
MS
Chiari malformation
Medical vertigo
Postural hypotension
Arrhythmia
Cardiac
Hypoglycemia and diabetes mellitus
Medication effects
Viral syndrome
Unlocalized vertigo syndromes
Anxiety and panic
Post-traumatic vertigo
Hyperventilation
Malingering
Unknown

vertigo diagnoses, the remainder being made up of individual unusual conditions (e.g., spinocerebellar degeneration).

1. **Basilar migraine** ordinarily presents with vertigo and headache, but it can also present as isolated vertigo. Migraine causes about 75% of central vertigo cases. It is particularly common in women in their 30s.
2. **Stroke and transient ischemic attack (TIA) involving the brainstem or cerebellum** causes about one-third of all central dizziness cases. Pure vertigo can occasionally be the only symptom preceding a posterior fossa stroke; there are no reliable means of distinguishing a TIA affecting the vestibular nucleus or cerebellum from another process affecting the vestibular nerve or end organ.
3. **Seizures** present with vertigo combined with motor symptoms or confusion. About 5% of central vertigo is caused by seizures. Dizziness is a common symptom in persons with known epilepsy.
4. **Multiple sclerosis (MS)** combines vertigo with other central signs such as cerebellar dysfunction. MS is an uncommon source of vertigo. About 2% of central vertigo cases are caused by MS. In persons with known MS, it is important not to attribute vertigo to MS without considering common peripheral causes that might be coincident, such as BPPV.
5. **The Chiari malformation** is a hindbrain malformation wherein the cerebellar tonsils herniate 5 mm or more below the foramen magnum. These patients complain of vertigo, ataxia, and occipital headaches, and often have downbeat nystagmus. Like SCD, symptoms may be precipitated by straining. MRI of the posterior fossa establishes the diagnosis. About 1% of cases of central vertigo are caused by the Chiari malformation.
6. **Cervical vertigo** is a controversial syndrome. Diagnosis is most often made after a whiplash injury where findings usually include vertigo, tinnitus, and neck pain. Examination usually demonstrates a nonspecific symptom complex including neck movement limited by pain and nausea or vertigo on neck positioning. Generally, there is no strong nystagmus even using video-recording methods. There are no definitive clinical or laboratory

tests for cervical vertigo. MRI of the cervical spine in these patients often shows cervical disks abutting but not compressing the cervical cord. Rare cases have been reported in whom vertigo can be traced to compression of a vertebral artery after neck rotation. Due to the lack of clarity in the diagnosis of cervical vertigo, its prevalence is unknown.

C. **Medical vertigo** may be caused by altered blood pressure, low blood sugar, and/or metabolic derangements associated with medication or systemic infection. It is largely encountered in the emergency room, where it accounts for about 33% of all cases of dizziness. It is unusual in subspecialty settings (2% to 5%). Table 16.1 lists nearly all causes of dizziness reported in studies of vertigo as it presents to emergency rooms.

1. **Postural hypotension** often presents as giddiness, lightheadedness, or syncope. Dizziness occurs only while the patient is upright.
2. **Cardiac arrhythmia** presents with syncope or drop-attacks. Like those of postural hypotension, symptoms are characteristically present only when patients are upright.
3. **Hypoglycemia** and metabolic derangements associated with diabetes present with giddiness or lightheadedness. Hypoglycemia is often accompanied by autonomic symptoms such as palpitations, sweating, tremors, or pallor. Together they account for about 5% of the cases of dizziness in general medical settings.
4. **Medication effects** usually presents with giddiness or lightheadedness, but also can present with true vertigo. These diagnoses account for about 16% of the dizzy patients seen in the emergency setting, but are rare outside the emergency room. Medications commonly implicated include antihypertensive agents, especially α-1 adrenergic blockers such as terazosin, calcium channel blockers such as nifedipine, and sedatives. Benzodiazepines, such as alprazolam, can cause dizziness as part of the withdrawal syndrome. Alcohol intoxication can present as a transient positional nystagmus, cerebellar signs, and direction changing positional nystagmus.
5. **Viral syndromes** not involving the ear are the reported cause of dizziness in approximately 4% to 40% of all cases seen in the emergency room setting. Such syndromes include gastroenteritis and influenza-like illnesses.

D. **Unlocalized vertigo** patients include those whose symptoms are attributed to psychiatric disorders, those whose symptoms are attributed to events without further definition (such as head trauma), and those with vertigo and dizziness of unknown origin. Common variants of unlocalized vertigo include psychogenic vertigo, hyperventilation syndrome, post-traumatic vertigo, and nonspecific dizziness. Between 15% and 50% of all patients with dizziness or vertigo fall into this category, depending both on referral base and diagnostic diligence.

1. **Unknown (nonspecific dizziness).** Diagnostic procedures are insensitive, and in dizziness evaluations it is usual to have as many as 50% of patients without any detectable abnormalities on careful clinical examination and thorough testing. Some authors wrongly define psychogenic vertigo as the complaints of patients falling into this category. About 75% of the unlocalized vertigo category consists of patients in whom there are no abnormalities on examination and testing.
2. **Psychogenic.** Patients with anxiety disorders, panic disorder, and post-traumatic stress disorder may complain of dizziness, ataxia, and autonomic symptoms. This is a common presentation. It is often impossible to determine whether or not anxiety is the sole cause or a reaction. In somatization disorder, symptoms may be present without anxiety.
3. **Post-traumatic vertigo** patients complain of vertigo following head injuries but frequently present no findings on examination or vestibular testing. BPPV is excluded by several negative Dix–Hallpike maneuvers using an adequately sensitive technique—e.g., video goggles. Post-traumatic vertigo is common.
4. **Hyperventilation syndrome.** These patients have vertigo after hyperventilation, without other findings or nystagmus. Hyperventilation-induced symptoms are commonly seen in well-documented structural abnormalities such as acoustic neuroma.
5. **Multisensory disequilibrium of the elderly.** Most elderly people have age-related multisensory impairment. Like the diagnosis of psychogenic vertigo, this diagnosis is often used in situations where examination is otherwise normal.
6. **Malingering.** Because vertigo can be intermittent and disabling, and frequently follows head injury, it may be claimed in an attempt to obtain compensation. Malingering is common only among patients who are being compensated for illness.

II. CLINICAL MANIFESTATIONS

A. Primary symptoms. The primary symptoms listed in Table 16.2 are mainly the result of a disturbed sensorium.

1. Vertigo denotes a sensation of rotation—either of the person or of the world. It can be horizontal, vertical, or rotatory. It can be described as visual "blurring" or "jumping." Horizontal vertigo is the most common type, usually resulting from dysfunction of the inner ear. Vertical vertigo is rarer. When transient, it is usually caused by BPPV. When constant, it is usually of central origin and accompanied by downbeat or upbeat nystagmus. Rotatory vertigo is the least frequent. When transient, rotatory vertigo is usually caused by BPPV. When chronic, it is always central and usually accompanied by rotatory nystagmus.
2. Impulsion denotes a sensation of translation, usually described as brief sensations of being pushed or tilted. Variants include rocking, floating, and perceived changes in the directions of up and down. Impulsion indicates dysfunction of the otolithic apparatus of the inner ear or central processing of otolithic signals. It is often a symptom of Ménière's disease.
3. Oscillopsia is an illusory movement of the world evoked by head movement. Patients with bilateral vestibular loss are unable to see when their heads are in motion because of oscillopsia. Patients with unilateral vestibular loss often complain that "the world doesn't keep up" when they rapidly rotate their heads laterally to the side of the bad ear.
4. Ataxia, unsteadiness of gait, is nearly universal in patients with otologic or central vertigo and is variably observed in patients with medical and unlocalized vertigo.
5. Hearing symptoms. Vertigo is often accompanied by tinnitus, hearing reduction or distortion, and aural fullness.

B. Secondary symptoms include nausea, autonomic symptoms, fatigue, headache, and visual sensitivity. Visual sensitivity is also known as the "grocery store syndrome." Patients complain of dizziness related to the types of patterned visual stimulation that occur when they view grocery store aisles, drive past picket fences or through bridges, or view large screen movies. The grocery store syndrome is a nonspecific common late symptom in patients with vertigo and is generally thought to be caused by a reweighting of sensory input related to balance (ear, eye, and body) resulting in greater dependence on vision.

C. Giddiness, wooziness, heavy-headedness, and lightheadedness. These terms have no precise meanings in common usage. They are rarely used by patients with documented inner ear dysfunction but are frequently used by patients with vertigo related to medical problems.

TABLE 16.2 Symptoms in Patients with Dizziness and Vertigo

Primary symptoms
Vertigo
Impulsion and rocking
Oscillopsia
Ataxia
Hearing symptoms
Secondary symptoms
Nausea, emesis, diarrhea
Pallor, bradycardia
Fatigue
Headache
Visual sensitivity
Nonspecific symptoms
Giddiness
Lightheadedness

III. EVALUATION

A. History. The history must either be all-encompassing or follow a heuristic technique whereby questions are selected as the interview progresses. Here we outline the all-encompassing approach.

1. **Definition.** Does the patient complain of vertigo (spinning), a secondary symptom (such as nausea), a nonspecific symptom (giddiness or lightheadedness), or something entirely different (e.g., confusion)?
2. **Timing.** Are symptoms constant or episodic? If episodic, how long do they last?
3. **Triggering** or exacerbating factors are listed in Table 16.3. All patients should be queried regarding these factors, either by going through them one by one, or by using an interview heuristic whereby one attempts to rule in or rule out a symptom complex (see IV).
4. **Otologic history.** Ask about hearing loss, tinnitus, and fullness. Positives are indications for an audiogram. Ask about the type of tinnitus—"roaring" tinnitus suggests Ménière's disease.
5. **Medication history.** Numerous medications can induce dizziness, including ototoxic drugs, antiepileptic drugs, antihypertensives, and sedatives. All current medications, as well as previous exposure to ototoxic agents, should be considered as sources of dizziness.
6. **Family history.** Has anyone in the immediate family had similar symptoms? Is there a family history of migraines, seizures, Ménière's disease, or early-onset hearing loss?
7. **Review of systems** should explore psychiatric problems (anxiety, depression, and panic), vascular risk factors, cancer, autoimmune disease, neurologic problems (migraine, stroke, TIA, seizures, and MS), otologic surgery, and general medical history (especially thyroid dysfunction, diabetes, Lyme's disease, or syphilis).
8. **Previous studies** relevant to dizziness (see III.C) should be reviewed.

B. Physical examination. The physical examination of the vertiginous patient is outlined in Table 16.4. It is ordered in such a way that procedures may be added on the basis of previous results. Because a full examination may be lengthy, it is most practical to expand or contract the examination dynamically. As an exception to the following procedure, if there is a history of positional vertigo, it is best to go immediately to the Dix–Hallpike test (see III.B.5.b).

1. **General examination.** Measure the blood pressure and pulse with the patient standing. Arrhythmia is noted, if present. If the standing blood pressure is low, check blood pressure with the patient lying flat. The heart, the carotid, and subclavian arteries are auscultated.
2. **Balance** is assessed via observation of gait (see Chapter 8), and the eyes-closed tandem Romberg's test. The tandem Romberg's test is extremely useful. Low-normal performance consists of the ability to stand heel-to-toe, with eyes closed, for 6 seconds. Young adults should be able to perform this test for 30 seconds, but performance declines with age.

TABLE 16.3 Triggering or Exacerbating Factors

Positional changes of head or body
Standing up
Rapid head movements
Walking in a dark room
Loud noises
Coughing, nose blowing, sneezing, or straining
Underwater diving, elevators, airplane travel
Exercise
Shopping malls, narrow or wide-open spaces, grocery stores
Foods (salt and monosodium glutamate)
Fasting
Alcohol
Menstrual periods
Boat or car travel
Anxiety or stress

It is helpful to develop a judgment of how much ataxia is appropriate for a given degree of ear injury. Patients with bilateral vestibular loss are moderately ataxic—they make heavy use of vision and are unsteady when their eyes are closed (with a narrow base). No patient with bilateral loss can stand in the eyes-closed tandem Romberg's test for 6 seconds. Patients with an additional superimposed position sense deficit are unsteady with eyes open (with a narrow base). Patients with chronic unilateral vestibular loss show very little ataxia, and they are usually normal on the eyes-closed tandem Romberg's test. The need to gauge ataxia does not come up in patients with recent unilateral vestibular imbalance because these patients have prominent nystagmus. Patients with cerebellar disorders, such as alcoholic cerebellar degeneration, have greater ataxia than is appropriate for their degree of nystagmus or vestibular paresis. Patients who are malingering also typically emphasize imbalance, which is the disabling aspect of their symptoms.

In head injury or where there is other reason to suspect a CNS origin of imbalance, also test basal ganglia function (pulsion/retropulsion tests).

3. **Otologic examination.** A brief screening test is adequate for hearing. The examiner's thumb and first fingers are rubbed together at arm's length from one of the patient's ears. Persons with normal hearing can perceive this sound at an arm's length. If the sound is not perceived, the source is brought in closer and closer until it is heard, and the distance is recorded. This simple test identifies high-tone hearing loss—for example, most elderly are able to hear at about 6 inches on either side. The tympanic membranes should be inspected for wax, perforation, otitis, discoloration, and mass lesions. Wax should be removed before more sophisticated diagnostic procedures are performed.

TABLE 16.4 Examination Procedures for Dizziness and Vertigo

Procedures	Triggers for Additions
General examination	
Orthostasis	
Arrhythmia	
Balance assessment	
Observe gait	
Eyes-closed tandem Romberg's test	
Pulsion and retropulsion	Parkinsonian gait
Otologic examination	
Hearing	
Tympanic membranes	
Neurologic examination	
Cranial nerves	
Long tract signs	
Cerebellar	
Position sense testing	Fails Romberg's test
Nystagmus assessment	*("g" indicates requires Frenzel's goggles)*
Spontaneous nystagmus (use ophthalmoscope if goggles are not available)	
Vibration test (g)	
Vertebral artery test (g)	Dizziness with neck discomfort
Dix–Hallpike positional test	
Head-shake test (g)	Negative exam so far
Valsalva's test (g)	Pressure sensitivity complex of symptoms
Hyperventilation (g)	Negative exam so far
VOR gain assessment	
Dynamic illegible "E" test	Fails Romberg test
Ophthalmoscope test	Fails "E" test

Procedures in italics are always performed; procedures not in italics are performed only for certain symptom complexes.

4. **Neurologic examination.** An abbreviated neurologic examination is adequate. It usually is convenient to check the vestibulo–ocular reflex (VOR) and nystagmus with the ophthalmoscope at this point (see III.B.5.a and III.B.6.b).
5. **Nystagmus** indicates an inner ear, brain, or (rarely) an ocular muscle disorder. Evaluation of nystagmus optimally require use of Frenzel's goggles, which are goggles worn by the patient to obscure their vision and magnify the examiners view of their eyes. Of the two Frenzel's goggle variants available, optical and video, the video goggles are far superior. Without a method of viewing the eyes without fixation, almost all nystagmus procedures are either useless or very insensitive. If you use Frenzel's goggles, mention this in your report. If you do not, indicate in your report that Frenzel's goggles were not available.
   a. **Spontaneous nystagmus** with Frenzel's goggles placed on the patient the eyes are observed for spontaneous nystagmus for 10 seconds. The typical nystagmus produced by inner ear dysfunction is a primary position "jerk" nystagmus—the eyes slowly deviate off center and then there is a rapid "jerk," which brings them back to the center position. Most nystagmus of other patterns (e.g., sinusoidal, gaze-evoked, and saccadic) are of central origin.

      If Frenzel's goggles are not available, similar information about spontaneous nystagmus can be obtained from the ophthalmoscopic exam. One simply monitors movement of the back of the eye. As the back of the eye moves oppositely to the front of the eye, for horizontal and vertical movement, one must remember to invert the direction of the nystagmus when making notes. Fixation can be removed by covering the opposite eye. Inner ear nystagmus is increased by removal of fixation. Congenital nystagmus is reduced by removal of fixation.
   b. **Dix–Hallpike positional test (Fig. 16.1).** The patient is positioned on the examination table so that, on lying flat, the head extends over the end of the table. The patient is then moved rapidly to the head-hanging position. If no dizziness or nystagmus is appreciated after 20 seconds, the patient is sat back up. The head is then repositioned to 45° right, and the patient is brought down to the head-right supine position. After another 20 seconds, the patient is sat up again, and the procedure is repeated to the left (head-left position). One hopes to see a burst of nystagmus provoked by either the head-right or the head-left position. The nystagmus of the most common type of BPPV (posterior canal) beats upward and has a rotatory component, such that the top part of the eye beats toward the down ear. The nystagmus typically has a latency of 2 to 5 seconds, lasts 5 to 60 seconds, and is followed by a downbeat nystagmus when the patient is sat up. There are also variant BPPV's with different vectors. The lateral-canal variant of BPPV is associated with a strong horizontal nystagmus that changes direction between head left and right. The anterior canal variant is associated with a downbeating nystagmus elicited by the Dix–Hallpike. **The remainder of the nystagmus tests require video Frenzel's goggles.**
   c. **Head-shake test.** Performed if there is no spontaneous nystagmus or positional nystagmus. Wearing Frenzel's goggles, the patient's head is rotated by the examiner in the horizontal plane, back and forth, for 20 cycles. One aims for a 45° excursion of the head to either side and a frequency of 2 cycles per second. A nystagmus lasting 5 seconds or more is an indication of an organic disorder of the ear or CNS and supports further investigation.
   d. **Neck vibration test.** The vibration test is more helpful than the head-shaking test. The eyes are observed in complete darkness while vibration is applied to the sternocleidomastoid for 10 seconds, first on one side and then on the other. A strong, direction-fixed nystagmus indicates a compensated peripheral vestibular lesion. The nystagmus beats away from the lesion.
   e. **Vertebral artery test for cervical vertigo.** With the patient upright and wearing the goggles, the head is rotated to the end of rotation on either side and left there for 10 seconds. The eyes remain in the center. A positive test consists of a nystagmus provoked by the position of the head on trunk. Positives are very rare.
   f. **Valsalva's test** is performed if there is a pressure sensitivity symptom complex on history (see IV). Although wearing the goggles, the patient takes a deep breath and strains for 10 seconds, while being observed for nystagmus with Frenzel's goggles. A positive test consists of nystagmus at the onset and release of pressure.

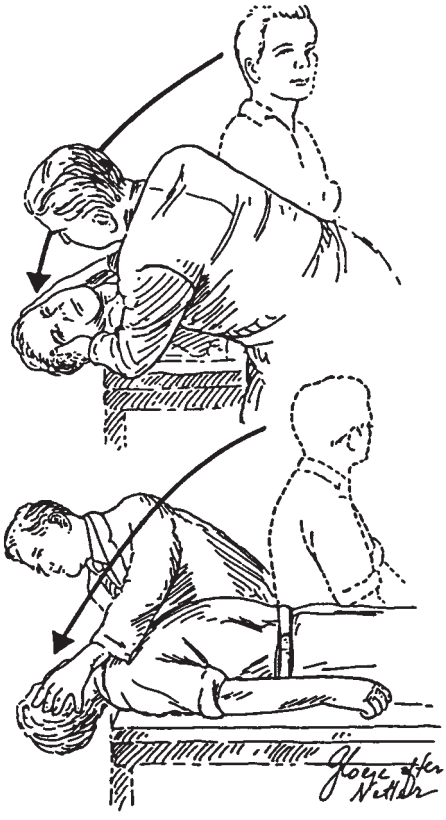


FIGURE 16.1 Dix–Hallpike positional test. To precipitate the characteristic nystagmus of BPPV, the patient is rapidly brought into a head position that makes the posterior canal vertical and also brings it through a large angular displacement. (From Baloh RW, Honrubia V. *Clinical Neurophysiology of the Vestibular System*. 2nd ed. Philadelphia, PA: Davis; 1990:124.)

g. **The hyperventilation test** is performed if so far the examination has been entirely normal. The patient takes 30 deep, hard breaths. Immediately after hyperventilation, the eyes are inspected for nystagmus with the Frenzel's goggles and the patient is asked if the procedure has reproduced the symptoms. A positive test without nystagmus suggests the diagnosis of hyperventilation syndrome. Nystagmus induced by hyperventilation suggests a partially conducting eighth nerve or central vestibular pathways, such as due to a tumor of the eighth cranial nerve, gamma knife radiosurgery, or MS.

6. **Assessment of VOR gain.** These maneuvers are aimed at documenting bilateral vestibular loss. They need not be done unless the patient has failed the eyes-closed tandem Romberg's test.
   a. The dynamic illegible "E" test. Using an eye chart at a distance of at least 10 ft, preferably calibrated in LogMar units, visual acuity is recorded with the head still. Then the examiner gently moves the patient's head horizontally at roughly 1 Hz, ±30°, and visual acuity is again recorded. Normal subjects drop from 0 to 2 lines of acuity with head movement. Patients with partial to complete bilateral loss of vestibular function drop from 3 to 7 lines of acuity. Patients with acute complete bilateral loss usually drop 7 lines of acuity.
   b. The ophthalmoscope test is done when the illegible "E" test is positive, to obtain objective corroboration. The examiner focuses on the optic disk and then gently moves the head as described above. If the disk moves with the head, this confirms that the VOR gain is abnormal. This test is less sensitive than the illegible "E" test.

C. Laboratory studies. Table 16.5 enumerates laboratory procedures commonly used for evaluation of patients with vertigo and dizziness, with indications. For efficiency and cost containment, procedures should be selected according to specific symptom complexes and be done sequentially. Algorithms are discussed in Sections IV and V.

1. **Audiologic testing** is indicated when there are hearing complaints. If the diagnosis is uncertain audiometry is recommended even for patients who have no hearing abnormalities.
   a. Audiogram. The audiogram measures hearing. Abnormalities suggest otologic vertigo.
   b. **Otoacoustic emissions (OAEs)** measure sounds generated by the ear itself. This is a quick and simple automated procedure. OAEs are useful in detecting malingering, central hearing deficits and persons with auditory neuropathy. In these situations, OAEs may be preserved even when subjective hearing is poor. When there is a potential for malingering, audiologists have at their disposal a large assortment of objective hearing tests that can generally detect psychogenic hearing loss. OAEs are usually not helpful in persons older than 60 years old, as OAEs are reduced with age.
   c. **Electrocochleography (ECOG)** is an evoked potential in which the recording electrode is positioned on the ear drum. It requires hearing. An abnormal ECOG is suggestive of Ménière's disease. ECOGs are difficult to perform and should not be relied upon for diagnosis by themselves.
2. **Vestibular testing** is not needed for every dizzy patient. The primary study—the electronystagmography (ENG) test—is helpful when there is no clear diagnosis after history and examination.
   a. **ENG** is a battery of procedures that can identify vestibular asymmetry (such as that caused by vestibular neuritis) and document spontaneous or positional nystagmus (such as that caused by BPPV). It is a long and difficult test, with little standardization,

TABLE 16.5 Laboratory Procedures for Dizziness and Vertigo

Test	Indication
Audiologic tests	
Audiogram	Vertigo, hearing symptoms
OAEs	Hearing symptoms, secondary gain
ECOG	Secondary test for Ménière's disease
Vestibular tests	
VEMP	Vertigo
ENG	Vertigo
Rotatory chair test	Bilateral loss, secondary to confirm ENG
Posturography	Secondary gain
Blood tests	
FTA-ABS	Vertigo with hearing symptoms
Glycohemoglobin	Hydrops symptom complex
ANA	Hydrops symptom complex
TSH	Hydrops symptom complex
Lyme serology	Vertigo in person from endemic area
Radiologic tests	
MRI of head	Central vertigo, abnormal BAER
MRA, vertebrobasilar	TIA
CT scan of temporal bone	Pressure sensitivity or Tullio's sign with asymmetrical VEMP, mastoiditis, congenital abnormality, significant head trauma
Other tests	
EEG	Quick spins, head trauma
Ambulatory event monitoring (Holter's monitoring)	Cardiogenic syncope
Tilt table test	Syncope

and an abnormal result that does not fit the clinical picture should be confirmed by rotatory chair testing, ideally in combination with VEMP testing.

b. **VEMP testing** is rapidly being deployed as a "basic" vestibular test because it provides a good balance between diagnostic utility and patient tolerability. They are sensitive to SCD syndrome, bilateral vestibular loss, and acoustic neuroma. VEMPs are generally normal in vestibular neuritis and Ménière's disease.

c. **Rotatory chair** testing measures vestibular function of both inner ears together. It is highly sensitive and specific for bilateral loss of vestibular function. In unilateral loss, it is sensitive but nonspecific. Also, it does not identify the side of the lesion.

d. **Posturography** is an instrumented Romberg's test. It is very useful in documenting malingering and also has utility in following the progress of persons undergoing treatment.

3. **Blood tests** are triggered by specific symptom complexes (see IV), and there is no "routine" set obtained for every dizzy patient. In particular, chemistry panels, CBCs, glucose tolerance tests, and allergy tests need not be routinely ordered.

4. **Radiologic investigations.** Skull films, cervical spine films, CT scans of the head, and CT scans of the sinuses are not recommended routinely in the evaluation of vertigo.

   a. **MRI scan of the brain** evaluates the structural integrity of the brainstem, cerebellum, periventricular white matter, and eighth nerve complexes. MRI is not routinely needed to evaluate vertigo without other accompanying neurologic findings (Chapter 32).

   b. **CT scan of the temporal bone** provides higher resolution of ear structures than MRI and also is better for evaluating lesions involving bone (see Chapter 32). Temporal bone CT is required to diagnose SCD. The "high resolution direct coronal" variant of this scan is best suited for this diagnosis. The temporal bone CT scan involves considerable radiation and for this reason VEMP testing is recommended as an initial screening test for SCD.

5. **Other tests.**

   a. **EEG** is used to diagnose seizures. Yield is very low in dizzy patients (Chapter 33).

   b. **Ambulatory event monitoring, or Holter's monitoring**, is used to detect arrhythmia or sinus arrest. Yield is high in persons with episodic orthostatic symptoms, lacking orthostatic hypotension.

   c. **Tilt table testing** is sometimes advocated for the diagnosis of neurocardiogenic syncope. When abnormal, treatment should focus on maintenance of blood pressure.

IV. DIFFERENTIAL DIAGNOSIS

We will now discuss symptom complexes, their differential diagnosis, and algorithms used to narrow down the differential. Table 16.6 enumerates five specific symptom complexes. When a patient does not fit into a complex in Table 16.6, one may fall back to grouping patients by duration of symptoms only, as in Table 16.7.

A. **Approach based on specific symptom complexes.**

1. **Bed spins and positional syndromes.** Patients complain of a brief burst of rotatory vertigo when getting into or out of bed, or on rolling over from one side to the other. This symptom strongly suggests the diagnosis of BPPV.

   a. **BPPV.** If a typical nystagmus is observed on Dix–Hallpike positional testing, no other diagnoses need be considered. Because roughly 95% of all positional nystagmus is caused by BPPV, even in cases in which an atypical positional nystagmus is observed, it is usually most efficient to try one of the currently available treatments before considering other diagnoses. Brain MRI is indicated when an atypical BPPV is refractory to treatment.

   b. **Central disorders.** Strong positional nystagmus may also accompany brainstem and cerebellar disorders (e.g., medulloblastoma and the Chiari malformation). Brain MRI is indicated when positional nystagmus is combined with an abnormal neurologic examination or when an atypical BPPV is refractory to treatment.

   c. **Vestibular neuritis.** A weak horizontal positional nystagmus may be found in peripheral vestibulopathies. ENG and audiogram are indicated.

TABLE 16.6 Specific Symptom Complexes

Positional vertigo (bed spins)
- BPPV
- Central vertigo
- Vestibular neuritis
- Postural hypotension

Headaches and vertigo
- Basilar migraine
- Post-traumatic vertigo
- Chiari malformation

Unlocalized vertigo
- Hydrops symptom complex (fluctuating hearing loss, vertigo, tinnitus and ear fullness)
- Ménière's disease
- Perilymphatic fistula (PLF)
- Post-traumatic hydrops
- Syphilis

Pressure sensitivity symptom complex
- Superior canal dehiscence (SCD)
- Perilymphatic fistula (PLF)
- Ménière's disease
- Chiari malformation
- Stapes malformation or prosthesis

Medicolegal situations
- Malingering and disability evaluations

TABLE 16.7 Typical Duration of Selected Conditions Causing Dizziness

1–3 seconds (quick spins)
- Vestibular nerve irritation
- BPPV variants
- Ménière's disease variants
- Epilepsy

Less than 1 minute
- BPPV
- Cardiac arrhythmia
- Ménière's disease variants

Minutes to hours
- VB TIA
- Ménière's disease
- Panic attacks, situational anxiety, hyperventilation
- Orthostasis

Hours to days
- Ménière's disease
- Basilar migraine

2 weeks or more
- Vestibular neuritis and labyrinthitis
- Central vertigo with structural lesion
- Anxiety
- Malingering
- Bilateral vestibular paresis or loss
- Multisensory disequilibrium of the elderly
- Drug intoxications

d. **Postural hypotension** also presents with dizziness on getting out of bed, but never occurs in bed. It is diagnosed by a symptomatic decrease in blood pressure between the supine and standing positions. A drop of 20 mm of mercury is significant.

2. **Headaches and vertigo.**
   a. **Migraine.** One large group of patients is women in their 30s with perimenstrual exacerbations. Food triggers, motion sickness, and positive family history are frequent associations. There is a weak association between BPPV and migraine, and the diagnosis of migraine-associated vertigo should prompt consideration of BPPV. Empirical trials of antimigraine medication may be the only way to make this diagnosis.
   b. **Post-traumatic vertigo.** Audiometry, ENG, and CT scan of the head are indicated.
   c. **Chiari malformation.** The headache is occipital, and there is downbeat nystagmus and ataxia. Diagnosis is from sagittal T1-MRI of the brain.
   d. **Unlocalized vertigo.** Audiometry and ENG are indicated for the vertigo component. The headache component (tension, migraine, sinus, etc.) is considered separately.
3. **Hydrops.** Patients complain of spells of vertigo, roaring tinnitus, and transient hearing loss, preceded by aural fullness. Audiometry should be obtained in all patients, as well as fluorescent treponemal antibody absorption test (FTA-ABS), sedimentation rate, and thyroid-stimulating hormone (TSH) blood tests.
   a. **Ménière's disease.** Usual duration of vertigo is 2 hours, but it can vary from seconds to weeks. Audiometry is crucial to document the fluctuating low-tone sensorineural hearing loss (Fig. 16.2). The diagnosis of Ménière's disease is highly probable when a typical history is obtained and when a fluctuating hearing loss is documented. ECOG testing may be performed in difficult cases, in an attempt to "rule in" the diagnosis. About 10% of all cases of bilateral Ménière's disease are autoimmune. Thyroid disease and/or migraine are very frequent in patients with Ménière's disease.
   b. **Perilymph fistula (PLF).** Occasionally, fistula presents with hydrops rather than the pressure sensitivity symptom complex (see IV.A.4). The only clue may be a history of barotrauma.
   c. **Post-traumatic hydrops** is a variant of the Ménière's disease symptom complex that appears after a significant blow to the ear, with presumed bleeding into the inner ear.
   d. **Syphilis.** Hearing loss is bilateral. Diagnosis is by FTA-ABS.
4. **Pressure sensitivity.** Patients complain of dizziness or ataxia evoked by nose blowing, high-speed elevators, cleaning of the ear with a cotton swab, straining as at stool, after the landing of an airplane, or after diving. In addition to pressure sensitivity, patients report vertigo induced by loud noises (Tullio's phenomenon) and by exercise. Patients

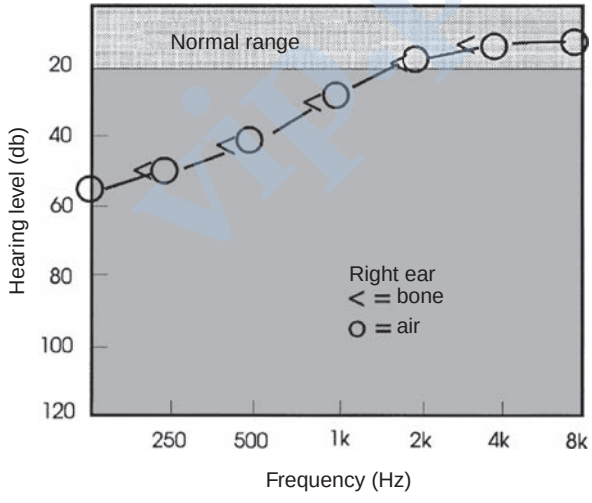


FIGURE 16.2 Low-tone hearing loss. A unilateral low-frequency sensorineural pattern hearing loss is often observed in early Ménière's disease.

are often extremely motion-intolerant and visually sensitive. Audiometry and the VEMP test are indicated.

a. **SCD** syndrome is the main source of pressure sensitivity. Vertigo and nystagmus can be provoked by loud noise or pressure. This syndrome is caused by dehiscence of bone overlying the superior semicircular canal. VEMP testing is nearly always abnormal due to asymmetry. Diagnosis is made by a high-resolution CT scan of the temporal bone.
b. **PLF.** Most patients have a history of barotrauma in they were unable to "clear" their ear during scuba diving or airplane travel. Audiometry and ECOG are indicated. A trial of a "ventilation" tube in the suspect ear is often helpful.
c. **Ménière's disease.** Mild pressure sensitivity occurs in about one-third of patients with Ménière's disease. See the hydrops symptom complex description (IV.A.3) for a differential diagnosis.
d. **Chiari malformation and platybasia.** Vertigo is correlated with straining but not with pressure in the external ear canal. The downbeat nystagmus and abnormal MRI found in the Chiari malformation also separate it from the other entities.
e. **Stapes malformation.** Remarkable pressure sensitivity with torsional movement of the eye occurs in patients with congenital malformations of the stapes footplate and also in patients in whom stapes prostheses (for otosclerosis) of excessive length have been inserted. A high-resolution CT scan of the temporal bone is indicated in this situation.

5. **Medicolegal situations.** The possibility of malingering often comes up in disability evaluations, worker's compensation cases, and legal situations where patients may potentially be compensated for being vertiginous. These patients usually present no objective evidence on physical examination or testing. Often they may resist examination, by closing their eyes at inappropriate times or refusing to perform key positional maneuvers. Their complaints often cannot be resolved into one of the symptom complexes discussed above. Objective testing (audiometry, OAE, ENG, VEMP, and an MRI scan of the head) is nearly always appropriate. In addition, posturography may be helpful. This test can trick the malingering patient by presenting a series of protocols that gradually become more and more difficult. The malingerer who is trying to fail the posturography test will frequently perform equally poorly on the easy and difficult subtests, producing a "nonphysiologic" pattern.

B. Approach based on timing only. These categories (Table 16.7) are less useful for diagnosis than those based on symptom complexes, but can be used when patients do not fall into any category. As such, they form a clinical "fall back" strategy.

1. **Quick spins are brief spells (1 to 3 seconds) of true vertigo,** unaccompanied by secondary symptoms. EEG should be obtained. A trial of oxcarbamazepine may be helpful.
   a. **Vestibular nerve irritation** due to the microvascular compression syndrome or a residual from vestibular neuritis. Extremely frequent spells—50 per day—are possible. Hyperventilation may induce nystagmus seen with video Frenzel's goggles. Magnetic resonance angiography (MRA) occasionally documents compression of the brainstem by the vertebrobasilan (VB) arterial system but there are many false positives. If the EEG is normal, a good response to oxcarbamazepine confirms the diagnosis.
   b. **Ménière's disease variants.** Patients complain of "shocks" or "earthquake" sensations. Frequency of spells is daily at most. Hearing is often affected. For diagnosis, see hydrops symptom complex (IV.A.3).
   c. **BPPV variants.** Spells are of no more than daily frequency. Presumably, otoconial debris is caught on a canal wall and suddenly slips down. Diagnosis is by the Dix–Hallpike maneuver. It may take several visits to get a positive result.
   d. **Epilepsy.** Spells can be frequent (20 per day), and there is often a history of head injury. Cognitive impairment is frequent.
2. **Less than 1 minute.** These are mainly postural syndromes.
   a. **Classic BPPV.** If there is positional vertigo, this diagnosis is easy. However, poor "historians" may omit to mention that they have adopted sleeping strategies (e.g., two pillows) by which bed spins are avoided. BPPV can also be triggered by unusual head positions such as looking up at the "top shelf." Diagnosis is by the Dix–Hallpike maneuver.

b. **Cardiac arrhythmia.** The clue is usually that vertigo spells occur only while standing, and that lightheadedness is a more prominent symptom than spinning. Ambulatory event monitoring is the best method of documenting this problem. Holter's monitoring may be used in contexts where event monitoring is not available.
c. **Ménière's disease variants.** See IV.B.1.c.

3. **Minutes to hours.**
   a. **TIA.** Spells of pure vertigo lasting 2 to 30 minutes, of abrupt onset and offset, in a patient with significant vascular risk factors are diagnosed as VB TIA until proven otherwise. Suspicion is reduced if there is a positional trigger. MRA or CTA of the VB circulation is the most useful tests.
   b. **Ménière's disease.** The typical Ménière's attack lasts 2 hours. If there are hearing symptoms, see the hydrops symptom complex (IV.A.3). If not, be cautious about proposing this diagnosis. Sometimes the term "vestibular Ménière's disease" is used to denote episodic vertigo having the typical timing of classic Ménière's disease but without any ear symptomatology. It is presently unclear whether this entity exists, and there is no method of confirming this diagnosis.
   c. **Panic attacks**, situational anxiety, and hyperventilation may produce symptoms of this duration (minutes to hours). These patients ordinarily are not symptomatic during examination. A detailed history is the most useful diagnostic test. If hyperventilation reproduces symptoms in patients without other findings, the diagnosis is hyperventilation syndrome. If hyperventilation also induces nystagmus, MRI is indicated.
   d. **Cardiac arrhythmia and orthostasis. See above.**
4. **Hours to days.**
   a. **Ménière's disease.**
   b. **Migraine.** It is so common in the general population that even unusual variants, such as manifestation solely as a vertiginous aura or intractable motion sensitivity with nausea, are common. Diagnosis is suggested by age, female gender, positive family history, attacks provoked by usual migraine triggers, and sensitivity to multiple sensory triggers (e.g., light, sound, and motion).
5. **Two weeks or more.**
   a. **Vestibular neuritis.** Diagnosis is made by combining a long duration with spontaneous nystagmus or an abnormal ENG test. The ENG should document nystagmus or a significant vestibular paresis (a conservative criterion is a paresis of 40% or more). The VEMP test should be normal. After 2 months of vertigo, central vertigo becomes more likely and an MRI is indicated. For labyrinthitis, the diagnosis is made by combining the vestibular neuritis pattern with hearing symptoms. Audiometry, VEMP, erythrocyte sedimentation rate, and fasting glucose are indicated.
   b. **Central vertigo with a fixed structural CNS lesion.** This diagnosis should be considered when there are neurologic symptoms or signs accompanying vertigo. Central vertigo may be permanent. For example, the combination of a peripheral vestibular loss with a cerebellar lesion may occur after acoustic neuroma surgery. Nevertheless, acoustic neuromas are extremely uncommon sources of peripheral or central vertigo due to their rarity compared with disorders such as BPPV. MRI is the most effective method of diagnosis of central vertigo. There are no examination maneuvers that can reliably separate peripheral vertigo (such as due to vestibular neuritis) from a central vertigo that lacks any "central signs."
   c. **Anxiety.** With this duration of symptoms (2 weeks or more), patients may be complaining of vertigo in your office. If a patient is presently complaining of vertigo, but no spontaneous nystagmus is evident under Frenzel's goggles, if they are not taking vestibular suppressants, one may reasonably conclude that the vertigo is functional in origin. Patients with anxiety typically report that nearly every trigger factor in Table 16.4 exacerbate their symptoms. Interestingly, whereas most patients with inner ear problems report that stress makes their symptoms worse, patients with anxiety frequently claim that everything except stress triggers vertigo. A positive response to a trial of a benzodiazepine supports this diagnosis but does not establish it, because many organic vestibular disorders also respond well to these medications.

d. **Malingering.** Malingerers persist in reporting symptoms as long as necessary to accomplish their purpose of obtaining favorable court settlements or disability rulings. Posturography and neuropsychological testing is usually very abnormal. Objective tests of vestibular function such as VEMP and ENG are nearly always normal.
e. **Bilateral vestibular paresis or loss.** These patients universally fail the dynamic illegible "E" test and the eyes-closed tandem Romberg's test. Their ataxia is worse in the dark. On audiometry, hearing is usually normal. Rotatory chair testing is the best way to confirm this diagnostic impression.
f. **Multisensory disequilibrium** of the elderly is essentially an unlocalized vertigo in an elderly patient. If the diagnosis is accurate, this is usually a permanent condition.
g. **Drug intoxications.** Diagnosis depends on withdrawal of medications.

V. DIAGNOSTIC APPROACH

A. Perform history and examination as outlined in II and III.
B. Approximately 20% to 40% of patients are diagnosed immediately on examination.
1. BPPV patients on Dix–Hallpike maneuver (15% to 20% of vertigo population).
2. Orthostatic hypotension and fixed cardiac arrhythmia such as atrial fibrillation (2% to 5%).
3. Bilateral vestibular paresis or loss on dynamic illegible "E" test (5%).
4. SCD with positive Valsalva's test (0% to 2%).
5. Acute vestibular neuritis via spontaneous nystagmus (2% to 5%).
C. For the remaining patients, proceed as follows:
1. If patient fits into a symptom complex category, follow procedures presented in IV.A.
2. If patient does not fit into a symptom complex, follow procedures outlined in IV.B.
a. If symptoms are intermittent, follow procedures in IV.B.1–3.
b. Otherwise, if symptoms are constant, proceed as follows:
(1) If duration has been <2 weeks, treat symptomatically or simply reassure and have patient return if symptoms persist beyond 2 weeks.
(2) If duration has been >2 weeks, follow the procedures outlined in IV.B.

VI. REFERRALS

A. Otology.
1. Cerumen disimpaction and ear microscope examination. Ear wax can be safely removed with the examining microscope, a standard piece of otologic equipment.
2. Progressive or acute hearing loss has potential medicolegal ramifications, and otologic consultation should usually be obtained.
3. A perforated tympanic membrane or mass in the canal or behind the tympanic membrane may require referral for closure of the perforation or surgical management of the tumor.
4. Mastoiditis or chronic otitis media. These patients are commonly managed with a mixture of surgery, cleaning, antibiotics, and antiseptics that requires otologic supervision.
5. Surgical management of acoustic neuroma, Ménière's disease, fistula, SCD, and cholesteatoma. Surgical treatment for Ménière's disease has greatly improved in recent years due to greater use of low-dose gentamicin protocols.
B. Internal medicine.
1. Cardiac or blood pressure problems, especially arrhythmia.
2. Management of diabetes or thyroid dysfunction.
C. Psychiatry.
1. Patients with disabling anxiety or panic disorders.
D. Neuropsychology.
1. Patients who may be malingering.

E. Vestibular rehabilitation (physical therapy).

1. Treatment for BPPV if office or home treatment fails.
2. Video Frenzel's goggle exam (if examiner does not have this critical piece of equipment).

Recommended Readings

Baloh RW. *Dizziness, Hearing Loss, and Tinnitus*. New York, NY: Oxford University Press; 1998.
Baloh RW, Halmagyi GM, eds. *Disorders of the Vestibular System*. New York, NY: Oxford University Press; 1996.
Brandt T. Cervical vertigo—reality or fiction? *Audiol Neurootol*. 1996;1(4):187–196.
Drachman D, Hart CW. An approach to the dizzy patient. *Neurology*. 1972;22:323–334.
Fisher CM. Vertigo in cerebrovascular disease. *Arch Otolaryngol*. 1967;85:85–90.
Herr RD, Zun L, Mathews JJ. A directed approach to the dizzy patient. *Ann Emerg Med*. 1989;18:664–672.
Minor LB. Superior canal dehiscence syndrome. *Am J Otol*. 2000;21:9–19.
Nedzelski JM, Barber HO, McIlmoyl L. Diagnoses in a dizziness unit. *J Otolaryngol*. 1986;15:101–104.
Sloane PD. Dizziness in primary care. Results from the national ambulatory medical care survey. *J Fam Pract*. 1989;29:33–38.

CHAPTER

17 Approach to the Patient with Hearing Loss

Richard T. Miyamoto and Marcia J. Hay-McCutcheon

Hearing loss affects almost 17 in 1,000 children under the age of 18 and approximately 314 in 1,000 adults over the age of 65. It has been estimated that 28 million Americans have a hearing impairment. Hearing loss produces substantial communication problems and can be the presenting symptom of serious underlying medical disorders. A detailed medical and audiologic evaluation is required to establish a specific etiology and management plan.

I. ETIOLOGY

There are various and often complex causes of hearing loss. In many cases, particularly among children, the cause of the hearing loss may remain unknown or idiopathic even after an extensive medical and audiologic work-up.

A. Despite the diversity of patients and their presenting symptoms, the causes of hearing loss can be classified as **hereditary** or **acquired.** Occasionally, there is not a clear distinction between the two types. For example, there is a genetic predisposition for certain populations to be more susceptible to noise-induced hearing loss.

B. The **onset** of hearing loss is a useful indicator when describing the cause. Hearing loss is considered **congenital** when it was caused before birth, **perinatal** when the hearing loss occurs during birth or shortly thereafter, and **postnatal** when the onset of the hearing loss occurs more than a month after birth.

C. Nonorganic hearing loss may occur in children and adults and its prevalence varies depending on the clinical situation.

II. ANATOMY AND PHYSIOLOGY OF THE AUDITORY SYSTEM

The auditory system is divided into four anatomical regions: (1) the external ear, (2) the middle ear, (3) the inner ear, and (4) the central auditory pathway.

A. The **external ear** consists of the pinna and the external auditory canal. It collects and directs sound to the tympanic membrane. Because of its physical dimensions, the external ear provides an important resonance boost between 2,000 and 5,000 Hz, a frequency range that contributes to the perception of speech.

B. The **middle ear** consists of the tympanic membrane, three ossicles (malleus, incus, and stapes), two middle ear muscles (tensor tympani and stapedius), and the ligaments that suspend the ossicles in the middle ear cavity. The middle ear structures transmit acoustic energy from the external environment to the inner ear and serve as a mechanical transformer recovering energy that would otherwise be lost as sound is transmitted from a gaseous medium (air) to a liquid medium (endolymph). The middle ear structures compensate for this impedance mismatch between the air and liquid mediums. Specifically, the difference in the areal ratio between the relatively large tympanic membrane and the small oval window recovers a substantial portion of the energy lost. Additionally, energy is recovered through the lever action of the handle of the malleus; that is, the handle is slightly longer than the long process of the incus.

C. The **inner ear** is divided into the **vestibular portion** consisting of three semicircular canals as well as the utricle and saccule, and the **auditory portion** consisting of the cochlea. The semicircular canals provide information regarding angular acceleration, and

the utricle and saccule provide information regarding gravitational or linear acceleration. The vestibular system, coupled with the visual and proprioceptive systems, functions as the body's balance mechanism. The cochlea is the end organ of hearing and is a shell-shaped cavity placed within the bony labyrinth. This fluid-filled structure is divided into three sections via the basilar membrane and Riessner's membrane. These sections are the **scala vestibuli,** the **scala media** (housing the hair cells), and the **scale tympani.** With the displacement of the stapes, a wave of motion (i.e., **traveling wave**) moves up the basilar membrane resulting in displacement of the one row of inner hair cells and three rows of outer hair cells. Sitting on the top of the hair cells are tiny cells referred to as **stereocilia,** which make direct contact with the **tectorial membrane,** a structure directly above the hair cells. The shearing action of the stereocilia on the tectorial membrane results in the stimulation of the hair cells. This motion causes the opening and closing of channels, which allows ions to flow into and out of the hair cells, thereby beginning the neural transduction process. The stiffness and mass characteristics of the basilar membrane vary along its length, and therefore, the traveling wave envelope will reach a peak at different locations. This location corresponds to a specific frequency region equivalent to the frequency of the auditory stimulus. Thus the inner ear acts as a **low-pass filter** with high-frequency sounds encoded at the basal region of the cochlea and low-frequency sounds encoded at the apical region of the cochlea. This **tonotopic arrangement** is maintained throughout the central auditory system.

D. Central auditory system. The central auditory system consists of the auditory portion of the eighth cranial nerve, the cochlear nucleus, the trapezoid body, the superior olivary complex, the lateral lemniscus, the inferior colliculus, the medial geniculate body of the thalamus, and finally the auditory cortex. The level of neural complexity increases exponentially with each higher order neuron or central auditory nucleus.

III. MEDICAL EVALUATION

Evaluation of the auditory system is accomplished by obtaining a detailed history, performing a physical examination, and conducting audiologic tests. In selected cases, radiologic imaging may be indicated.

A. History. The otologic history includes inquiry into symptoms of ear disease, including hearing loss, ear pain (otalgia), discharge from the ear (otorrhea), tinnitus or other head noises, and vertigo or dizziness. If any of these symptoms are present, a detailed characterization is performed. The clinical significance of hearing loss is related to the time and acuity of onset, severity, and the tendency to fluctuate or progress. The deleterious effects of hearing loss are particularly great when the onset occurs before the development of spoken language (i.e., prelingual hearing loss).

B. Physical examination.

1. The **otologic examination** begins with inspection of the pinna and palpation of periauricular structures, including the periauricular and parotid lymph nodes.
2. **Otoscopic examination** of the external ear canal and tympanic membranes is performed to identify abnormalities of these structures. Pneumatic otoscopy is helpful in assessing the mobility of the tympanic membrane and is particularly useful in identifying a subtle middle ear effusion.
3. A complete **head and neck examination** is performed, including a cranial nerve and cerebellar testing.
4. **Tuning fork tests** are an important part of the otologic functional examination for hearing acuity. They are particularly useful in differentiation between conductive and sensorineural hearing loss. The most useful tuning forks are those with vibrating frequencies of 512 and 1,024 cycles per second. The 2 most commonly used tuning fork tests are **Weber's test** and **Rinne's test.**
   a. **Weber's test** is performed by placing the stem of the tuning fork on the midline plane of the skull. The patient is asked to identify the location of the auditory percept within the head. The signal lateralizes to the ear with conductive hearing loss provided normal hearing is present in the opposite ear. This occurs because the ambient

room noise present in the usual testing situation tends to mask the normal ear, but the poorer ear with a conductive loss does not hear such noise and better hears bone-conducted sound. If a sensorineural loss is present in one ear and the opposite ear is normal, the fork is heard louder in the better ear.

b. **Rinne's test** is performed by alternately placing a ringing tuning fork opposite one external auditory meatus and firmly on the adjacent mastoid bone. The loudness of the tuning fork in these two locations is compared. The normal ear hears a tuning fork about twice as long with air conduction as with bone conduction. Conductive hearing loss reverses this ratio, and sound is heard longer with bone conduction than with air conduction. Patients with sensorineural hearing loss hear better by means of air conduction than by means of bone conduction, although hearing is reduced with both air and bone conduction.

IV. AUDIOLOGIC EVALUATION

The audiologic evaluation characterizes the type, severity, and configuration of a hearing loss. Loss of hearing can be either partial or total. It can affect the low, middle, or high frequencies in any combination.

A. Range of hearing. Although the human ear is sensitive to frequencies between 20 and 20,000 Hz, the frequency range from 300 to 3,000 Hz is most important for understanding speech.

1. During an audiologic evaluation, pure-tone thresholds are routinely obtained for frequencies at octave intervals between 250 and 8,000 Hz.
2. The range of sound pressure to which the human ear responds is immense. Infinitesimal movement of the hair cells produces a just audible sound, yet a million-fold increase is still tolerable.
3. The large range of numbers needed to describe audible sound pressure is best represented by a logarithmic ratio comparing a sound to a standard reference sound. This is called the decibel. The decibel is defined in relation to the physical reference of sound, or sound pressure level, to the average threshold of normal hearing for young adults, or hearing level (HL), or to a patient's own threshold for the sound stimulus, or sensation level.
4. Speech sounds vary in their acoustic characteristics. Vowels tend to have most of their energy in the low to middle frequencies and are produced at relatively higher intensities than consonants. Thus vowels carry the power of speech. Consonants tend to contain higher frequency information and have low power. Much of the actual understanding of speech depends on the correct perception of consonants. Consequently, speech may not be audible for patients with hearing loss across the entire frequency range. Patients with hearing loss in the higher frequencies may hear speech but not understand it.

B. Audiogram. To graphically represent the degree of hearing, pure-tone thresholds are displayed on an audiogram (Fig. 17.1). On this graph, **frequency** (pitch) is represented on the horizontal axis and **intensity** (loudness) is presented on the vertical axis. The 0 dB HL line represents the average threshold level for a group of normal-hearing young adults with no history of otologic disease or noise exposure. Conversational speech at a distance of 1 m has an intensity level of approximately 50 to 60 dB HL. Speech becomes uncomfortable to listen to at approximately 80 to 90 dB HL.

C. Pure-tone threshold audiometry. The audiometric threshold is defined as the softest intensity level of a pure-tone signal that can be detected by the patient 50% of the time. Thresholds are generally obtained for air-conduction stimuli presented through earphones or in a sound field, and for bone-conduction stimuli presented with a vibrator placed on the mastoid or forehead.

For adults and older children, pure-tone testing simply requires a behavioral response to pure-tone stimulation. For infants older than 5 months, **visual reinforcement audiometry** can be used to obtain thresholds. In this operant discrimination task (i.e., yes–no paradigm), infants are trained to turn to their right or left when they hear a signal, where they see an illuminated animated toy. Alternatively, **play audiometry** is used to assess the hearing of preschool children. In this technique, play activities are used as operant reinforcers for a child's response to auditory signals.

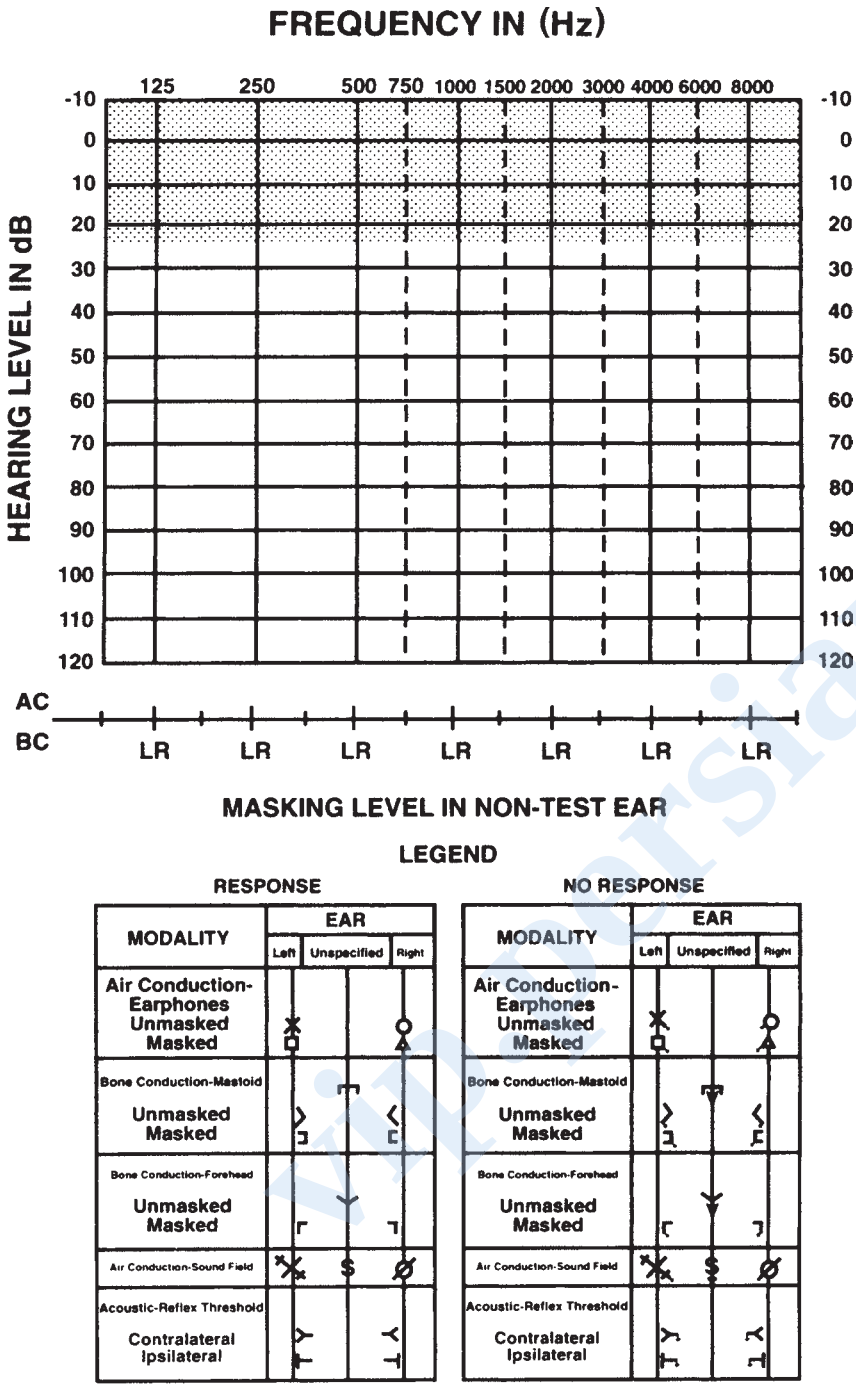


FIGURE 17.1 A sample audiogram. The *y*-axis represents the intensity level in dB HL and the *x*-axis represents the pure-tone frequency of the stimulus. The threshold is the softest level that the patient hears the pure-tone signal 50% of the time.

The **degree of hearing loss** is classified in terms of audiometric thresholds and are slight (16 to 25 dB HL), mild (26 to 40 dB HL), moderate (41 to 55 dB HL), moderately severe (56 to 70 dB HL), severe (71 to 90 dB HL), and profound (>90 dB HL).

D. **Speech audiometry.** Speech signals can be used to assess hearing sensitivity and the processing capabilities of the auditory system. For some patients, speech can be audible but not easily understood due to various physiologic and environmental factors. The following tests are designed to assess both the audibility and intelligibility of speech.

1. **Speech threshold tests.** A speech recognition threshold (SRT) and a speech awareness threshold (SAT) are used to examine sensitivity to speech. These tests can be obtained for each ear individually or for both ears via sound field testing. The SRT is obtained at the lowest intensity level at which the patient can *repeat* spondee words (i.e., two-syllable words with equal stress on each syllable) 50% of the time. The SAT is the lowest intensity level that allows the patient to *detect* the presence of speech. The SRT and the SAT are used to provide a valid estimate of hearing sensitivity and to verify the accuracy and reliability of the pure-tone thresholds. The SRT and pure-tone average of the thresholds obtained at 500, 1,000, and 2,000 Hz should be within ±7 dB of one another. If a discrepancy exists, the examiner should doubt the validity or accuracy of the patient's thresholds.
2. **Speech discrimination.** Word recognition or speech discrimination testing determines how well a patient can understand speech when the stimuli are presented at suprathreshold intensity levels. Speech recognition or discrimination scores depend on the type, severity, and configuration of the hearing loss and on the type of pathologic condition of the ear. The scores depend on a number of stimulus and response characteristics. The patient's attending and cognitive skills also can influence the results, particularly in examinations of children and elderly persons. Although several pathologic conditions can markedly decrease speech recognition or discrimination scores, a rollover phenomenon in which the scores first increase and then dramatically decrease with increasing presentation levels is a characteristic of retrocochlear lesions.

E. **Screening for hearing loss.** Because hearing is critical for speech and oral language development in children, early identification of hearing loss is a primary concern for health care professionals and educators. The **Joint Committee on Infant Hearing 2007 Position Statement and Guidelines** endorse universal hearing screening of newborn infants before 1 month of age. For infants who fail their initial screening, it is recommended that a comprehensive audiologic evaluation be completed by 3 months of age. For infants with a hearing loss, appropriate health care and educational provisions should be made by 6 months of age. It is also recommended that regular audiologic and communication screenings be conducted within the first 3 years of life for all children.

V. PHYSIOLOGIC MEASURES OF HEARING

Whenever possible, behavioral measures of hearing should be used to assess the status of the auditory system. However, due to many variables that can affect the validity and reliability of these measures, particularly when testing the hearing of infants and young children, physiologic techniques can be used to assess the integrity of the auditory system.

A. **Immittance audiometry** is an objective means for determining the integrity of the middle and external ear cavities and can provide information about middle ear pressure, the mobility of the tympanic membrane, eustachian tube functioning, the mobility of the ossicles, and acoustic reflex thresholds (ARTs).

1. **Tympanometry** is used to assess disorders of the middle ear that affect the tympanic membrane, middle car space, and ossicular chain. It provides information about the mobility of the tympanic membrane in response to changes in air pressure presented to the external auditory canal. **Tympanograms** typically present the amount of compliance as a function of air pressure and are classified as **Type A** (normal middle ear function—see Fig. 17.2), **Type B** (flat—no change in compliance with change in external ear canal pressure), or **Type C** (negative middle ear pressure that may indicate the presence of fluid in the middle ear). This testing, however, can lack specificity for infants younger than 6 months because of the high compliance of their external ear canal walls.

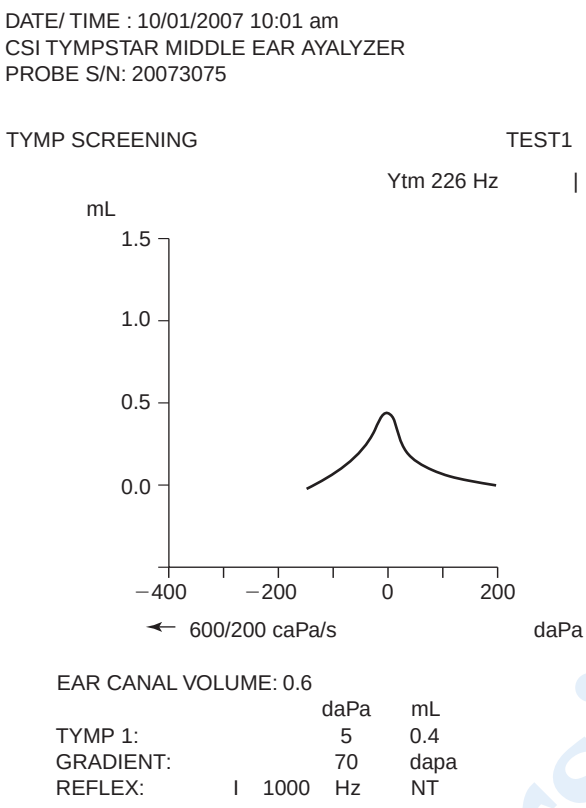


FIGURE 17.2 A sample normal (Type A) tympanogram. The compliance of the middle ear system is measured as a function of the presented pressure to the external ear.

2. **ART.** When an ear with normal hearing is exposed to an intense auditory signal, the stapedius muscle contracts. This contraction can be measured as changes in ear canal pressure. It can be elicited in normal hearing individuals using pure-tone signals that vary between 70 and 100 dB HL. The lowest intensity level that produces this response is referred to as the ART. This acoustic reflex occurs bilaterally regardless of which ear is stimulated, if the system is functioning normally. The presence or absence of the reflex and the intensity levels at which the reflex is obtained provide information useful in identifying lesions within the auditory system up to the level of the superior olivary complex.

B. Auditory brainstem response (ABR). This electrophysiologic response is generated by activation of the neurons within the eighth cranial nerve and lower auditory brainstem. Rapid, short-duration acoustic signals, such as a click stimulus, can elicit this response. Because these responses are relatively small in relation to the noise (both internal and external), signal averaging techniques are used to record the electrical response of the auditory system.

1. An example of an ABR is presented in Figure 17.3. The response is judged by the presence of positive waves (I, II, III, IV, and V) occurring within a specific latency range (i.e., the time after stimulus onset that a response occurs). The latency, amplitude, and morphologic features of the responses depend on the patient's age, the stimulus characteristics, and the recording parameters. Persons with normal peripheral ear and lower auditory brainstem system integrity have a response to clicks at intensities as low as 5 dB normal HL (nHL). When using click stimuli, the response is sensitive to the hearing status between 2,000 and 4,000 Hz. Different methods of evoked potential testing can be used

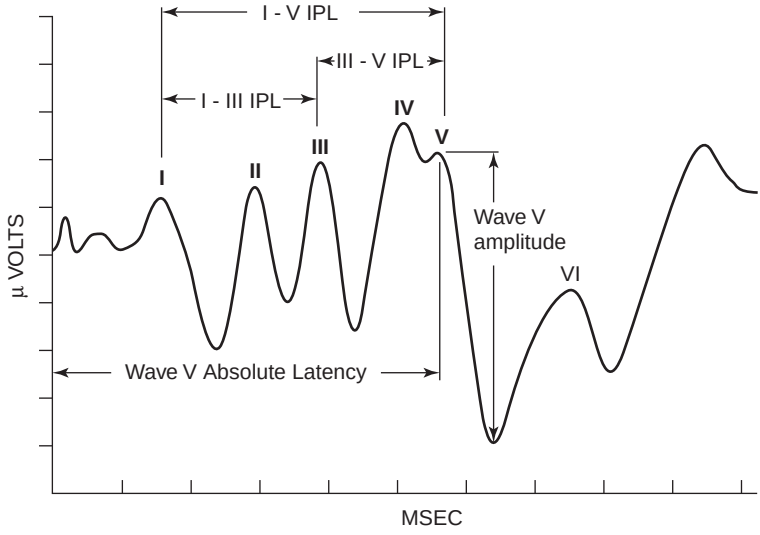


FIGURE 17.3 A sample ABR. Each wave in the response is identified using roman numerals (I, II, III, IV, and V).

to estimate hearing sensitivity outside this frequency range, but the results typically are less robust than the responses to click stimuli.

2. The test parameters and interpretation criteria for ABR depend on the nature of the questions asked by the clinicians. Because the amplitude measures are highly variable and more susceptible to artifacts, clinicians typically use latency measures to assess integrity of the system. When screening for hearing loss, the clinician examines the waveform for the presence of distinctive peaks, particularly wave V. As the intensity of the stimulus changes so to should the latency. The obtained latencies are compared with the normative values available for the type of patient. In the differential diagnosis of retrocochlear lesions, a prolonged wave I–V interpeak latency difference becomes the most sensitive indicator of this condition. Also, other prolonged interpeak latencies and interaural latency differences can be enough information for a diagnosis.
3. Although the click-evoked ABR can appear as early as the 25th week of gestation and is typically present at the 27th week of gestation, there are developmental changes in the response until approximately 2 years of age. The decrease in the absolute latency of the response is the most salient change during this maturational period. Therefore, interpretation of the ABR to identify hearing loss depends on age-appropriate norms. If wave V of the ABR is present in a test ear at 35 dB nHL, it is likely that the infant has normal hearing sensitivity between 2,000 and 4,000 Hz.

C. Auditory steady state responses (ASSR) are brain potentials that are evoked by steady-state stimuli as opposed to short-duration acoustic signals used to generate the ABR. The EEG activity recorded from scalp recording electrodes contain amplitude modulated (AM) and/or frequency modulations (FM) that follow the variations in the recording stimuli. The recorded responses are suspected to arise from the auditory nerve, the cochlear nucleus, the inferior colliculus, and the primary auditory cortex because neurons at these sites are responsive to AM and FM signals.

1. The presence or absence of the ASSR is determined using statistical analyses.
2. As with the ABR, the ASSR can be used to estimate audiometric thresholds. Data have suggested that the ASSR thresholds are correlated with the ABR thresholds. Additionally, there is evidence suggesting that the ASSR can be recorded from individuals with now measureable ABR. Consequently, this response has gained popularity as a tool for evaluating children who are being considered for cochlear implantation.

	Last name	First name	Ear	Date	Result	Protocol
☼	-	-	Left	01-Oct-07	Pass	2-6 kHz Screen, 4/6 for Pass
○	-	-	Right	01-Oct-07	Pass	2-6 kHz Screen, 4/6 for Pass

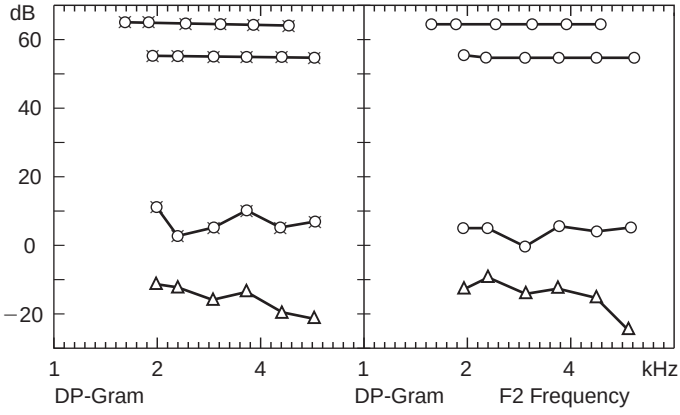


FIGURE 17.4 A sample DPOAE—gram. The left panel displays the results for the left ear (*x*'s), and the right panel displays the results for the right ear (*circles*). The triangles in both panels represent the level of the noise in the ear, and the uppermost lines in each panel indicate the level of signal presentation.

D. Otoacoustic emissions are sounds that are generated in the cochlea and propagate back through the middle ear and ear canal where they can be measured with a microphone. Hearing losses due to cochlear or middle ear lesions can be readily identified with otoacoustic emissions; however, these measurements do not define the severity of the hearing loss. There are two classes of otoacoustic emissions—spontaneous otoacoustic emissions and evoked otoacoustic emissions. Evoked otoacoustic emissions can be further divided according to the type of stimulus used during measurement—**stimulus frequency emissions, transient evoked otoacoustic emissions (TEOAEs),** and **distortion product otoacoustic emissions (DPOAEs).** Measurement of DPOAEs and TEOAEs are preferred for clinical purposes.

1. Figure 17.4 illustrates the DPOAE results from a normal hearing adult. DPOAEs are generated from the presentation of two pure-tone frequencies to the ear, which results in a third "distortion product" response. The nonlinearity nature of the cochlea is responsible for the distortion product. In the figure, the intensity of the response is displayed as a function of the response frequency. The left panel shows the results for the left ear and the right panel shows the responses for the right ear. The triangles in both panels represent the level of the noise and the upper most lines in each panel indicate the level of signal presentation.

VI. HEARING LOSS

It is broadly classified into two types—conductive and sensorineural—and each type has a wide variety of pathologic causes.

A. Conductive hearing loss occurs when sound cannot efficiently reach the cochlea. The blockage may be due to abnormalities of the ear canal, the tympanic membrane, or the middle ear ossicles, including the footplate of the stapes.

1. Hearing loss due to **obstruction of the external auditory canal** can result from impacted cerumen, foreign bodies in the canal, and swelling of the canal during infection. Cerumen impaction is the most common cause of conductive hearing loss. It is normally secreted by glands in the outer one-third of the cartilaginous portion of the ear

canal. Its function is to clean and lubricate the ear canal and also to provide protection from bacteria, fungi, and insects. Other obstructions include atresia (a complete closure of the ear canal), stenosis (a narrowing of the ear canal), collapsed ear canals, and bony growths within the ear canal.

2. Conductive hearing loss may result from damage to the tympanic membrane or middle ear as a result of trauma or infection. Perforation of the tympanic membrane and ossicular discontinuity are surgically correctable.
3. **Otitis media with effusion** is the most common cause of conductive hearing loss among children. This condition can be associated with adenoid hypertrophy. The middle ear effusion may necessitate treatment with myringotomy (i.e., creating a small incision in the tympanic membrane) and tube placement.
4. **Otosclerosis** is the most common cause of conductive hearing loss among individuals in the mid-childhood to late middle-adult years. Otosclerotic bone (i.e., growth of spongy bone) progressively fixes the stapes in the oval window. This condition can be successfully managed with a stapedectomy.

B. **Sensorineural hearing loss** results from lesions central to the footplate of the stapes that involve the cochlea or cochlear division of the eighth cranial nerve. When the site of lesion is within the cochlea, the hearing loss is considered sensory. When the site of lesion is within the auditory neural pathway, the hearing loss is neural or retrocochlear. In sensorineural hearing losses, both air- and bone-conduction thresholds are outside the normal range of hearing sensitivity.

1. **Hereditary.** Sensorineural hearing loss may be hereditary; at least 100 genetic syndromes that involve hearing loss have been identified. It has been estimated that 50% of childhood sensorineural hearing loss is due to genetic factors. Genetic forms of hearing loss may be congenital or delayed in onset, unilateral or bilateral, and progressive or sudden in nature.
2. **Infection.** A number of viruses, including cytomegalovirus, rubella, and herpes simplex, have been implicated as etiologic agents in congenital and acquired hearing loss. Congenital syphilis and bacterial meningitis are contemporary causes of deafness despite the greatly improved treatment options available.
3. **Neoplasm.** In patients with unilateral progressive sensorineural hearing loss, acoustic neuroma must be suspected. Bilateral acoustic neuroma is the hallmark of neurofibromatosis type 2 and must be suspected when a patient has a positive family history (autosomal dominant inheritance).
4. **Other common causes** of sensorineural hearing loss are noise exposure, metabolic and systemic changes in the auditory system, ototoxic medications, aging (presbycusis), and head trauma.

C. **Mixed hearing loss** exists when both conductive and sensorineural hearing losses occur in the same ear. The lesions are additive, resulting in marked air-bone gaps with the bone-conduction thresholds falling outside the normal range of hearing sensitivity.

D. **Auditory neuropathy/dyssynchrony.** Some patients have normal peripheral auditory systems up to and including the outer hair cells but have hearing difficulties. This condition can result from the absence of the auditory nerve, or more commonly, from dyssynchronous electrical responses that are sent to the brain from the auditory nerve. These patients present with a range of hearing sensitivities but typically have great difficulty understanding speech in degraded listening conditions. These patients typically have normal immittance results and normal otoacoustic emissions, yet they have anomalies in evoked potentials, particularly in the ABR, and in the behavioral response under earphones or in the sound field. The causes of auditory neuropathy/dyssynchrony vary among patients; however, the pathologic process most likely affects the inner hair cell or the auditory processing abilities of the auditory nerve and lower brainstem. Because of the possible dead regions in the cochlea or neural involvement, these patients do not respond typically to some of the traditional treatment protocols.

E. **Central auditory processing disorder.** Patients with this type of disorder have difficulty perceiving and appropriately using acoustic information because the central auditory system is incapable of adequately processing the signals transduced by the cochlea. Patients with central auditory processing disorders can be taught compensation

strategies to improve their ability to comprehend speech. Many adults with sensorineural hearing losses also may have a concomitant central auditory processing disorder, which confounds the evaluation and management of the sensorineural hearing loss.

VII. MANAGEMENT AND REFERRAL LISTS

When any hearing loss is suspected or identified, the patient should be referred for otologic examination and audiologic evaluation to determine the appropriate means of treatment. For conductive hearing loss, medical management is the primary course of treatment. Although many patients with sensorineural hearing loss require medical treatment and follow-up care, the primary course of management of this type of hearing loss is amplification, whether through hearing aids, cochlear implants, or assistive listening devices.

A. Amplification. Hearing aids differ in design, size, amount of amplification, ease of handling, volume control, and availability of special features. But they do have similar components, which include a microphone to pick up sound, amplifier circuitry to make the sound louder, a receiver to deliver the amplified sound into the ear, and batteries to power the electronic parts.

1. **Hearing aid styles.** The majority of hearing aids fall into one of four categories. The completely-in-the-canal hearing aid is the smallest and requires some form of automatic signal processing because it is difficult to manipulate controls, which are located deep inside the ear canal. The in-the-canal and in-the-ear aids sit outside the ear canal and allow manual manipulation of various controls on the hearing aid. The behind-the-ear hearing aid rests behind the ear and requires an earmold to direct the flow of sound into the ear. This style is often chosen for young children for safety and growth reasons.
2. **Hearing aid circuitry.** Hearing aids also are differentiated according to technology or circuitry. **Conventional analog** hearing aids are designed with a particular frequency response based on the audiogram. The hearing aid has a series of potentiometers that the dispenser can adjust to approximate the values of amplification needed by the user. **Analog programmable** hearing aids contain a microchip that allows the aid to have settings programmed for different listening environments, such as quiet conversation in the home, noisy situations as in a restaurant, or large areas such as a theater. **Digital programmable** hearing aids have all of the advantages of analog programmable hearing aids, but the dispenser also uses digital signal processing to change the characteristics of the signal to maximize its frequency and intensity characteristics to meet the user's needs at any given moment in time.
3. **Cochlear implants** are amplification devices used to fit children and adults who have severe and profound hearing losses. Although the external processor is similar to that of a digital hearing aid, the internal components of the cochlear implant directly stimulate the neural cells of the eighth cranial nerve. Sounds sent to the external microphone are processed via the speech processor and then sent directly to the internal electrode array that is placed within the scala tympani of the cochlea. The electrical pulses are directed toward the spiral ganglion cells and the auditory nerve. The peripheral ear, therefore, is completely bypassed with this form of stimulation. Previously, unilateral cochlear implants were commonly provided, but more recently, patients are being provided with bilateral implants. Additionally, some individuals with unilateral implants find the use of a hearing aid in the opposite ear to be beneficial for communication purposes.
4. **Assistive listening devices** are specialized listening systems that may or may not interface with hearing aids and cochlear implants. These devices are designed to augment communication function by improving the signal-to-noise ratio during degraded listening activities. The type of assistive listening device usually is designated by the type of transmission properties the device uses such as FM systems, infrared systems, loop (wire inductance) systems, and hard-wired systems. These devices are particularly effective for listening in large-group situations such as in classrooms, churches, or public meetings. They are also effective in bridging the gap between many audio devices, such as televisions and radios, with the user's hearing aids or cochlear implants.

B. Referral. The following organizations can assist the interested reader in locating patient education materials and appropriate otologic and audiologic service providers in their areas:

American Academy of Otolaryngology-Head and Neck Surgery
1650 Diagonal Road
Alexandria, VA 22314-2859
Phone: (703) 836-4444
Fax: (703) 683-3100
www.entnet.org

American Speech-Language-Hearing Association
10801 Rockville Pike
Rockville, MD 20852
Phone: (800) 638-8255
Fax: (240) 333-4705
www.asha.org

American Academy of Audiology
11730 Plaza America Drive, Suite 300
Reston, VA 20190
Phone: (800) AAA-2336, (703) 790-8466
Fax: (703) 790-8631
www.audiology.org

Recommended Readings

Brown CJ, Johnson TA. Electrophysiologic assessment of hearing. In: Cummings CW, Flint PW, Haughey BH, Richardson MA, Eds. Otolaryngology: Head and Neck Surgery. 5th ed. Philadelphia, PA. Mosby Elsevier; 2010: ch 134.

Dillon H. *Hearing Aids*. New York, NY: Thieme; 2001.

Durrant JD, Lovrinic JH. *Bases of Hearing Science*. 3rd ed. Baltimore, MD: Williams & Wilkins; 1995.

Gorga MP, Johnson TA, Kaminski JR, et al. Using a combination of click- and tone burst-evoked auditory brainstem response measurements to estimate pure-tone thresholds. *Ear Hear*. 2006;27:60–74.

Joint Committee on Infant Hearing. Year 2007 position statement: principles and guidelines for early hearing detection. *Pediatrics*. 2007;120:898–921.

Katz J. *Handbook of Clinical Audiology*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002.

Musiek FE, Rintelmann WF. *Contemporary Perspectives in Hearing Assessment*. Boston, MA: Allyn and Bacon; 1999.

Norton SJ, Gorga MP, Widen JE, et al. Identification of neonatal hearing impairment: evaluation of transient evoked otoacoustic emission, distortion product otoacoustic emission, and auditory brainstem response test performance. *Ear Hear*. 2000;21:508–528.

Pickles JO. *An Introduction to the Physiology of Hearing*. 2nd ed. New York, NY: Academic Press; 1988.

Ruenes R. *Otologic Radiology with Clinical Correlations*. New York, NY: Macmillan; 1986.

Schuknecht HF. *Pathology of the Ear*. 2nd ed. Philadelphia, PA: Lea & Febiger; 1993.

Souza PE, Tremblay KL. New perspectives on assessing amplification effects. *Trends Amplif*. 2006;10:119–143.

Speaks CE. *Introduction to Sound: Acoustics for the Hearing and Speech Sciences*. 3rd ed. San Diego, CA: Singular Publishing Group, Inc.; 1999.

Working Group on Cochlear Implants. Cochlear implants. ASHA technical report; 2004.

Yost WA. *Fundamentals of Hearing: An Introduction*. 3rd ed. San Diego, CA: Academic Press; 1994.

Zeng F-G. *Trends in Cochlear Implants*. *Trends Amplif*. 2004;8:1–34.

CHAPTER

18 Approach to the Patient with Dysphagia

Jeri A. Logemann

Dysphagia is common after sudden-onset neurologic damage such as stroke, head injury, or spinal cord injury. Oropharyngeal swallowing problems are also common in patients with degenerative neurologic disease such as motor neuron disease, amyotrophic lateral sclerosis and postpolio syndrome, myasthenia gravis, multiple sclerosis, or Parkinson's disease.

I. DYSPHAGIA: DIFFICULTY SWALLOWING

Dysphagia may be the first symptom of neurologic disease. It is critical to identify the presence of a swallowing problem early, define the exact nature of the physiologic or anatomic problem, and institute appropriate compensatory or therapy procedures to prevent costly medical complications (see I.B.4.).

A. Symptoms of oropharyngeal dysphagia.

1. Coughing at meals.
2. Struggling to eat.
3. Taking longer to eat.
4. Chronic excessive secretions including tracheal secretions, chronic bronchitis, and asthma.
5. Weight loss of unexplained origin.
6. Pneumonia, especially recurrent.
7. Gurgly voice quality, especially during or after meals.
8. Recurrent fevers or increased secretions within 1 to 1½ hours after meals.
9. Elimination of some consistencies of foods from the diet.
10. Difficulty managing own saliva.
11. Patient complaint of difficulty swallowing.

B. Effects of dysphagia on health and the health care system.

1. **Aspiration pneumonia.** A significant positive correlation has been found between the aspiration observed during a modified barium swallow (MBS) test and the development of pneumonia within the next 6 months.
2. **Malnutrition.**
3. **Dehydration.**
4. **Increased costs of health care** including hospitalization for aspiration pneumonia and other costly medical complications, nonoral feeding, nursing care, if dysphagia is not managed properly.

C. Prevention: The reason for the evaluation and treatment of oropharyngeal dysphagia. In patients with neurologic damage or disease, dysphagia cannot be prevented, but the expensive medical complications that result from swallowing disorders can be prevented as a result of appropriate assessment and treatment.

1. **Prevent expensive medical complications.** Aspiration pneumonia alone is a significant cost to the health care system.
2. **Facilitate the patient's return to safe and efficient oral intake.** Nonoral feeding requires greater nursing care and often specially prepared feedings, both of which are more costly than oral feeding.

II. NORMAL SWALLOWING

At all ages, normal swallowing is safe and efficient, moving food or liquid from the mouth, through the pharynx and into the cervical esophagus in 2 seconds or less, and through the esophagus in an additional 8 to 20 seconds.

A. Swallowing stages.

1. **Oral preparatory stage (variable duration)** includes chewing and other oral manipulations, which reduce food to a consistency appropriate for swallowing and provide taste and pleasure of eating. It does not depend on good dentition. Lip closure, circular and rotary action of the tongue, normal facial tone, and rotary jaw action are included in this stage of swallow. Oral tongue action and fine motor control of the tongue are most important because tongue action controls food in the mouth.
2. **Oral stage (lasts approximately 1 second).** The oral tongue is responsible for propelling food through the oral cavity and for providing sensory input contributing to triggering the pharyngeal stage of swallow.
3. **Pharyngeal triggering (takes half a second or less)** involves sensory input from the oral cavity to the cortex and brainstem, which is recognized as a swallow stimulus in the nucleus tractus solitarius in the brainstem. This sensory information is passed to the nucleus ambiguous, which triggers the pharyngeal motor response.
4. **Pharyngeal stage (lasts less than 1 second)** involves closure of the airway to prevent the entry of food into the airway (aspiration), opening of the upper esophageal sphincter (UES) to allow food to pass into the esophagus, and pressure applied to the bolus by the tongue and pharyngeal walls to clear food efficiently into the esophagus.
5. **Esophageal stage (lasts 8–20 seconds)** involves sequential contraction of the esophageal muscle fibers from top to bottom, propelling the bolus ahead of the contractile wave into the stomach. This phase also involves relaxation of the lower esophageal sphincter to allow the bolus to pass into the stomach.

B. Neuromuscular components of the normal swallow.

1. **Lip closure** is maintained from the time food is placed in the mouth until the pharyngeal swallow is completed. If lip closure cannot be maintained, the nasal airway may not be patent.
2. **Lingual control.** Oral tongue action is required in oral preparation because the tongue controls the food in the mouth during chewing. The tongue also forms the food into a ball or bolus in preparation for the swallow, subdividing the food in the mouth if necessary, to ensure the appropriate size bolus for swallowing. The oral portion of the tongue then propels the food through the oral cavity and into the pharynx.
3. **Rotary, lateral jaw motion.** Jaw action crushes the food, which is placed on the biting surfaces of the teeth by the tongue.
4. **Velar or soft palate elevation and closure of the velopharyngeal port** prevent food from entering the nasal cavity.
5. **Tongue base posterior motion.** Tongue base motion generates pharyngeal pressure on the bolus, as does sequential contraction down the pharyngeal wall.
6. **Airway closure** prevents aspiration. Airway closure begins at the true vocal folds, proceeds to the level of the airway entrance, that is, the false vocal folds, arytenoids, and base of epiglottis, and ends as the epiglottis is folded over the airway. The most critical level of airway closure is at the entrance, that is, the arytenoid cartilage and the base of epiglottis and false vocal folds. This level of closure prevents food from entering the airway.
7. **Opening of the UES** involves a complex set of actions including (1) relaxation of the cricopharyngeal muscular portion of the valve, which does not open the sphincter; (2) laryngeal upward and forward motion, which opens the sphincter by carrying the anterior wall of the sphincter, the cricoid cartilage, away from the pharyngeal wall; and (3) arrival of the bolus under pressure, which increases the width of the opening of the upper sphincter.
8. **Esophageal peristalsis** begins when the tail of the bolus enters the esophagus and follows the bolus through the esophagus.

C. Systematic changes in oropharyngeal swallow with changes in volume and viscosity of the incoming food and voluntary control. Not all swallows are alike. Normal

oropharyngeal swallow physiology changes systematically as the volume and viscosity of the food being swallowed increases. A great deal of voluntary control can also be exerted over the oropharyngeal swallow. These systematic changes help to explain why patients have more difficulty with one type of food than another. The swallows are, in fact, different for different foods.

1. **As bolus volume increases,** the duration of the oral and pharyngeal stages of the swallow increases. The duration of airway closure and cricopharyngeal opening increases systematically.
2. **Increasing viscosity** of food increases the width of cricopharyngeal opening.
3. **Volitional control** also changes the characteristics of the oropharyngeal swallow.
   a. Breath-holding can extend the duration of airway closure at the vocal folds or at the entrance to the airway. This is often done in anticipation of swallowing a large volume of liquid, as from a cup.
   b. Volitional control can open the UES and prolong the duration of UES opening.
   c. Volitional control can extend the duration and extent of laryngeal elevation.
   d. Increasing effort during swallow will increase oropharyngeal pressures. Voluntary changes can occur spontaneously as patients "work" to swallow or patients can be taught these as compensations for swallowing problems.

D. Effects of normal aging.

1. Oral transit time slows 0.5 to 1.0 seconds with increasing age, probably because older adults most often hold the bolus on the anterior floor of the mouth and must pick it up with their tongue to begin the swallow.
2. Slightly slower shift from the oral to pharyngeal stage in individuals over age 60, probably because of slower neural processing.
3. After age 80, range of motion of pharyngeal structures is reduced, that is, there is less muscle reserve and less flexibility in the swallow. This is particularly true in men.
4. Over age 60, esophageal peristalsis becomes less efficient.
5. Healthy elderly individuals do not aspirate more often than young people. Elderly patients (over age 80) who become generally weak and sick will demonstrate a weak swallow because of their reduced muscular reserve. This can cause aspiration.

E. Efficiency and safety.

1. Normal swallows are efficient, moving food quickly through the mouth and pharynx and into the esophagus (under 2 seconds).
2. Only occasional aspiration occurs, usually when the mechanism is stressed or when both eating and talking in a social situation.
3. Efficiency and safety do not change significantly with age.

III. SWALLOWING DISORDERS

Swallowing disorders can occur in any stage of swallow and may involve one or more of the neuromuscular actions or sensory inputs described earlier as involved in the swallow.

A. Swallowing disorders can be **anatomic** or **physiologic** in nature.

B. Effective treatment of swallowing disorders requires identification of the specific anatomic and/or physiologic abnormalities in each patient's swallow, such as reduced laryngeal elevation, poor airway closure, and reduced tongue base movement.

C. Aspiration and inefficient swallowing causing oral or pharyngeal residue are symptoms of swallowing disorders. They are not disorders. These symptoms will disappear when the patient's swallowing physiology returns to normal.

IV. DEFINITIVE ASSESSMENT OF THE OROPHARYNGEAL SWALLOW: THE MBS

A. An MBS is performed by a speech–language pathologist and a radiologist. This radiographic (videofluorographic) test examines the anatomy and physiology of the oral and

pharyngeal stages of swallowing. These stages must be examined separately from the esophagus, which is anatomically and physiologically distinct from the oral cavity and pharynx and requires a different technique for assessment **(a barium swallow).** An MBS assessment examines the ability of the pharynx to manage small to large volumes and thin to thick viscosities of food. An esophageal assessment requires presentation of a large amount of liquid in order to distend the esophagus, which as a collapsed muscular tube cannot be examined adequately unless distended.

1. **Purpose.**
   a. Defines oral and pharyngeal swallow physiology in relation to patient's swallow symptoms.
   b. Defines swallow physiology symptomatic of neurologic disease.
   c. Examines effectiveness of management strategies designed to assist patients in continuing to eat safely by mouth or to begin eating safely by mouth.
   d. Defines a treatment plan to rehabilitate oropharyngeal swallow physiology and to eliminate symptoms of dysphagia including aspiration, thereby preventing the development of aspiration pneumonia.
   e. Defines safest and most efficiently swallowed diet (food consistencies).
2. **Procedure** (designed to minimize risk of aspiration by presenting calibrated small to larger amounts of liquid, pudding, and masticated material as tolerated by the patient).
   a. Patient seated upright initially and examined in the lateral plane to define speed, efficiency, and safety (aspiration) of the swallow.
   b. Liquids given in 1-, 3-, 5-, or 10-ml cup drinking amounts (2 swallows each) to observe "dose response" of the pharynx and to define optimal volume for each patient.
   c. If and when the patient aspirates or has a highly inefficient swallow, various treatment strategies are provided and their effects observed radiographically, including:
      (1) Posture changes.
      (2) Increased sensory input.
      (3) Therapy procedures (requires normal cognition).
      (4) Increased bolus viscosity. Nectar or honey-thickened liquids as needed if thin liquids are aspirated and no other strategy is effective.
   d. Pudding (1–2 ml) and a small bite of cookie are given (2 swallows each) as tolerated by patient.
   e. The patient is turned and examined in the anteroposterior plane to define symmetry of the swallow.
   f. The report contains a description of the oral and pharyngeal anatomy and swallow physiology causing the patient's dysphagia symptoms, identification of the types and amounts of foods safely swallowed, whether or not partial or full nonoral feeding is possible, and the effectiveness and need for compensatory strategies or swallow therapy.
3. **Reevaluation.** To ensure patient safety, the patient's oropharyngeal swallow may need to be reevaluated when the patient appears ready to move to oral intake.

B. **Barium swallow** is used to examine the esophageal stage of swallowing, particularly esophageal anatomy and any anatomic abnormalities such as stricture and tumors. Because this assessment requires the patient to swallow larger volumes of liquid, it should be completed after an oropharyngeal assessment, that is, the MBS, to be sure the patient can safely tolerate these larger volumes.

1. Assesses esophageal anatomy and peristaltic action.
2. Misses reflux disease 60% to 80% of the time.

V. SCREENING TESTS FOR OROPHARYNGEAL DYSPHAGIA

These tests are not definitive and tend to overidentify patients at risk for swallowing disorders in the pharyngeal stage of swallowing.

A. **A bedside or clinical exam** usually performed by a speech–language pathologist. A bedside or clinical, noninstrumental assessment of swallowing cannot reliably define swallow physiology or dysphagia symptoms such as aspiration.

1. Complete medical history including history of the swallowing problem.
2. Complete oromotor test of lip, jaw, tongue, pharyngeal, and laryngeal function.
3. Trial swallows of small amounts of food are observed.

B. The Toronto Bedside Swallowing Screening Test. A validated test of the presence of dysphagia in stroke patients. Does not define the nature of the swallowing disorders.

VI. PATIENTS WITH KNOWN NEUROLOGIC DAMAGE OR DISEASE WITH COMPLAINTS OF SWALLOWING PROBLEM(S)

A. Progressive neurologic disease. Dysphagia is frequent in progressive neurologic disease at some point in the patient's deterioration. Many neurologic diseases can first present with swallowing difficulties including Parkinson's disease, motor neuron disease, postpolio syndrome, myasthenia gravis, multiple sclerosis, Guillain–Barré's syndrome, and stroke.

1. **Parkinson's disease.**
   a. Swallowing problem may come early or later in disease progression.
   b. Patient may aspirate silently, that is, there is no cough.
   c. Symptoms of swallowing disorder.
      (1) Patient may slow down while eating (because of characteristic [pathognomonic] rocking, rolling tongue motion).
      (2) Patient may swallow two or three times with each bite of food because the swallow is not efficient and there is residue in the pharynx.
      (3) Increased chest secretions, "bronchitis" with chronic cough, which are actually signs of chronic aspiration.
      (4) Gurgly voice quality because of residual food remaining at the top of the airway.
   d. **Referrals.**
      (1) MBS.
      (2) Swallowing therapy as indicated by MBS.
   e. **Progression** is slow and may worsen very slowly over 10, 20, or more years.
   f. **Parkinson medications** may improve swallowing disorder in some patients.
   g. **Swallow therapy.** The patient responds moderately well.
2. **Amyotrophic lateral sclerosis.**
   a. A swallowing or speech disorder may be first symptom and usually affects oral stage of swallow first with reduced tongue strength and fine control so that chewing is increasingly difficult.
   b. **Symptoms** of swallowing disorders.
      (1) **Diet change.** The patient eliminates foods from their diet requiring chewing, thicker foods requiring more muscle effort to swallow.
      (2) **Weight loss.**
      (3) **Coughing** usually occurs when swallowing liquids, which are not controlled well by the tongue and splash into the pharynx and into the open airway.
      (4) There may be **some aspiration.**
   c. **Referrals.** MBS at regular intervals (3 to 4 months) for patients with brainstem involvement to define best eating strategies. Direct exercise fatigues muscles.
   d. **Progression.**
      (1) Often rapid in predominantly brainstem involved patients. Patient may be advised to stop eating and accept gastrostomy when within 1½ to 2 years of diagnosis because of chronic aspiration.
      (2) Very slow in patients with predominantly spinal involvement. It may be 10 to 15 years before dysphagia is severe enough to cause weight loss or chronic aspiration.
3. **Postpolio syndrome.**
   a. Dysphagia may begin as patients reach their 40s or 50s, particularly patients with a history of bulbar polio.
   b. The patient may have **reduced awareness** of the swallow problem.
   c. Symptoms of a swallowing disorder.

d. **Referrals.** An MBS is indicated to define optimum eating strategies. Often the problem is unilateral weakness in the pharynx and head rotation toward the damaged side of the pharynx during eating facilitates improved clearance of food. Direct exercise fatigues the mechanism.
e. **Progression** is slow, worsening over years.

4. **Myasthenia gravis.**
   a. A swallow or speech disorder may be the first symptom.
   b. **Symptoms** may include the following:
      (1) Fatigue in selected muscles of mouth or pharynx as eating progresses. May become severe enough so that no swallowing is possible.
      (2) Increasing nasality, hoarseness, imprecision in speech sounds as the patient continues to talk.
   c. **Referrals.** An MBS is used to define involved musculature and extent of fatigue.
   d. **Progression.** Slow worsening of symptoms. Medication may significantly improve swallowing.
5. **Multiple sclerosis.**
   a. Swallowing problem may be first symptom, but is more likely to occur as the disease progresses. The patient is often unaware of the swallowing problem.
   b. Wide range of swallowing disorders as various parts of the nervous system are affected.
   c. **Symptoms** may include the following:
      (1) Difficulty swallowing liquids with coughing because of pharyngeal swallow delay.
      (2) Complaint of food "stuck in the throat" because of reduced strength of tongue base and pharyngeal wall movement.
   d. Responds well to **swallowing therapy.**
   e. **Referrals.**
      (1) MBS.
      (2) Swallowing therapy, if indicated by results of MBS.

B. Sudden onset neurologic disorders. Stroke, head injury, and spinal cord injury may cause dysphagia from which the patient has potential for recovery with appropriate management. The focus of management should be early radiographic assessment (MBS) with swallowing therapy to prevent medical complications from occurring. The more medical problems and complications the patient sustains, the longer the recovery.

1. **Stroke.** Single or multiple strokes can cause swallowing problems.
   a. A **single infarct** in the cortex, subcortical region, or brainstem can cause swallowing problems to worsen within the first week post stroke. By 3 weeks post stroke, patients usually will be functional swallowers unless they are taking medications that may affect swallow or have additional medical complications that slow swallowing recovery.
   b. **Brainstem stroke** patients are at greatest risk for dysphagia. Some brainstem stroke patients, particularly those with lateral medullary syndrome, will need intensive swallowing therapy.
   c. Patients with **multiple strokes** often exhibit more severe swallowing problems and require more rehabilitation, but usually do recover to full oral intake.
   d. **Referrals.**
      (1) An MBS when the patient is alert and awake (3 to 4 days post stroke) to determine need for nonoral feeding and swallowing therapy. Repeat study at 3 weeks post stroke to determine progress and discontinue nonoral feeding if no longer needed.
      (2) Swallowing therapy, if indicated by MBS.
2. **Head injury.** Approximately one-third of the patients with head injury exhibit swallowing problems. Dysphagia may result from the neurologic injury, from other injuries to the head or neck, such as laryngeal fractures, and from acute care procedures, such as long-term intubation. Usually, neuromuscular damage is present in both the oral and pharyngeal phases of swallowing.
   a. **Referrals.**
      (1) MBS.
      (2) Swallowing therapy, if indicated by MBS.
   b. Most patients regain oral intake with therapy. Some patients who are severely head injured will require maintenance therapy from a caregiver to maintain safe and adequate oral intake.

3. **Cervical spinal cord injury.** Patients with cervical spinal cord injuries who undergo anterior spinal fusions are at greatest risk for dysphagia. The pharyngeal swallow is usually impaired.
   a. **Referrals.**
      (1) MBS.
      (2) Swallowing therapy.
   b. Most often swallowing problems are in the pharyngeal phase of the swallow.
   c. With swallowing therapy, most patients will recover. The length of time in recovery will depend on the extent of physical damage and the number of medical complications sustained.

VII. PATIENTS WITH COMPLAINTS OF SWALLOWING DISORDER(S) (DYSPHAGIA) BUT NO MEDICAL DIAGNOSIS

A. Most often these patients have a progressive neurologic disease, have had a stroke, or have a brain tumor. Rarely does the dysphagia indicate a head or neck cancer. Rarely is dysphagia a psychogenic problem. Anatomic or physiologic disorders should be ruled out first before psychogenic etiology considered.

B. Testing Needed.

1. **History.** A complete medical and swallowing history should be taken, including:
   a. **Pattern** of difficulty.
      (1) Fatigue at the end of the meal could indicate myasthenia gravis.
      (2) Foods that the patient finds difficult.
      (3) Gradual or sudden onset. If gradual onset, usually indicates neurologic disease. Sudden onset may indicate a stroke.
   b. **Family history** of any swallowing problem.
2. **Symptoms.** Asking the patient to describe their symptoms is helpful.
   a. Food remains in mouth—indicates oral stage problem.
   b. Food hesitates at the top of neck—may indicate difficulty triggering pharyngeal stage.
   c. Food remains in throat—may indicate pharyngeal stage problems.
   d. A feeling of pressure at the base of the neck or a feeling that food remains at base of neck—usually indicates an esophageal stage problem.
   e. Pressure, feeling of food caught in chest—usually indicates esophageal stage problem(s).
3. **Other motor signs.**
   a. **Gait changes.**
   b. **Tremor** in the tongue, jaw, pharynx, or larynx. Tremor at rest may indicate Parkinson's disease.
   c. **Speech or voice changes.** Many patients with neurologic disease may exhibit speech and/or voice changes and swallowing problems.

VIII. SUMMARY

Early MBS assessment by a speech–language pathologist can reduce the medical complications from dysphagia and thereby reduce costs to the health care system. One hospitalization for aspiration pneumonia can equal the cost of MBSs and follow-up swallowing therapy for 3 to 5 patients for 3 months. Careful and aggressive management of dysphagia can save the health care system significant costs in hospitalization and other medical costs.

Recommended Readings

Buchholz D. Clinically probable brainstem stroke presenting primarily as dysphagia and nonvisualized by MRI. *Dysphagia.* 1993;8:235–238.

Horner J, Massey EW, Riski JE, et al. Aspiration following stroke: clinical correlates and outcomes. *Neurology.* 1988;38:1359–1362.

Lazarus CL, Logemann JA, Rademaker AW, et al. Effects of bolus volume, viscosity and repeated swallows in normals and stroke patients. *Arch Phys Med Rehabil.* 1993;74:1066–1070.

Logemann JA. Head and neck diseases in the elderly: effects of aging on the swallowing mechanism. *Otolaryngol Clin North Am.* 1990;23(6):1045–1056.

Logemann JA. The dysphagia diagnostic procedure as a treatment efficacy trial. *Clin Commun Disord.* 1993;3(4):1–10.

Logemann JA. *A Manual for Videofluoroscopic Evaluation of Swallowing.* 2nd ed. Austin, TX: Pro-Ed; 1993.

Logemann JA. *Evaluation and Treatment of Swallowing Disorders.* 2nd ed. Austin, TX: Pro-Ed; 1998.

Logemann JA, Kahrilas P, Kobara M, et al. The benefit of head rotation on pharyngoesophageal dysphagia. *Arch Phys Med Rehabil.* 1989;70(10):767–771.

Logemann JA, Pauloski BR, Rademaker AW, et al. Temporal and biomechanical characteristics of oropharyngeal swallow in younger and older men. *J Speech Lang Hear Res.* 2000;43:1264–1274.

Martino R, Silver F, Teasell R, et al. The Toronto Bedside Swallowing Screening Test (TOR-BSST): development and validation of a dysphagia screening tool for patients with stroke. *Stroke.* 2009;40(2):555–561.

CHAPTER

19 Approach to the Patient with Dysarthria

Sarah S. Kramer, Michael J. Schneck, and José Biller

Normal speech production involves the integration and coordination of five primary physiological subsystems: respiration, phonation, articulation, resonance, and prosody. Impairment of any of these elements may lead to dysarthria or slurring of speech. Dysarthria may occur secondary to lesions along the neuroaxis that produce motor dysfunction of any of these five speech systems. Lesions can be unilateral or bilateral and localize to the cerebral cortex, subcortical structures, brainstem, cerebellum, basal ganglia, cranial nerves, upper cervical nerves, or even the neuromuscular junction or musculature.

I. DEFINITION

Dysarthria is defined as "difficult, poorly articled speech resulting from interference in the control and execution over the muscles of speech usually caused by damage to a central or peripheral motor nerve." Dysarthria is a group of speech disorders characterized by muscle control disturbance leading to impaired articulation of sounds. The words are slurred, but the language content is normal. Dysarthria should be differentiated from mutism, dysphonia, aphasia, and apraxia of speech.

II. CLINICAL PICTURE

A normal speech pattern is achieved through the smooth coordination of respiration, phonation, articulation, resonance, and prosody. Adequate breath support and forced exhalation gives way to changes in vocal fold length, position, and vibratory pattern. As exhalation occurs, changes in the size and shape of the oral cavity in conjunction with the articulators produce phonemes for speech production. At the same time, changes in prosody attach meanings to phonemes with alterations in pitch, intonation, stress, and rate. Together, these speech mechanisms allow us to effectively participate in daily conversation. The semiology of dysarthria may include: slurred speech, slow or rapid speech, whispering speech, abnormal intonation, and changes in quality such as nasal or hoarse sounding speech, breathy sounding speech. Associated clinical findings include limited or abnormal movements of the tongue, jaw or lips, drooling, and difficulty chewing or swallowing.

III. TYPES OF DYSARTHRIA

Differentiating among the dysarthrias is not simple as there is much overlap in the semiology of the various types of dysarthia, although certain speech characteristics are often associated with specific types of dysarthria. The flaccid, spastic, mixed, ataxic, hypokinetic, and hyperkinetic dysarthria are best characterized and described below (see also Table 19.1):

A. Flaccid dysarthria, as seen in bulbar palsy, is characterized by excessive hypernasality. Articulation of consonants and/or vowels is imprecise with slow and labored speech rate. It is typically caused by damage to cranial nerves V (motor division), VII, X, and XII that supply muscles of articulation and mastication. Muscle weakness, hypotonia, and/or atrophy may be observed. One common cause of flaccid dysarthria is idiopathic seventh nerve (Bell's) palsy. Often these patients complain of changes in speech, drooling, and oral dysphagia. The face may appear asymmetrical during range of motion tasks even if normal at rest.

TABLE 19.1 Mayo Clinic Classification of Dysarthria

Dysarthria Type	Neurologic Condition	Location of Lesion	Most Distinctive Speech Deviation
Flaccid	Bulbar palsy	LMN	Marked hypernasality, often with nasal air emission; continuous breathiness; audible inspiration
Spastic	Pseudobulbar palsy	UMN	Very imprecise articulation; slow rate; low pitch; harsh strained or strangled voice
Ataxic	Cerebellar ataxia	Cerebellum	Excess stress and monostress; phoneme and interval prolongation; dysrhythmia of speech and syllable repetition; slow rate; some excess loudness variation
Hypokinetic	Parkinsonism	Extrapyramidal system	Monopitch, monoloudness, reduced overall loudness; variable rate; short rushes of speech; some inappropriate silences
Hyperkinetic 1. Quick	Chorea	Extrapyramidal system	Highly variable pattern of imprecise articulation; episodes of hypernasality; sudden variations in loudness
	Myoclonus		Rhythmic hypernasality; rhythmic phonatory interruption
	Tourette syndrome		Sudden tic-like grunts, barks, coprolalia
2. Slow	Athetosis	Extrapyramidal system	No distinct deviation
	Dyskinesias	Extrapyramidal system	No distinct deviation
	Dystonia	Extrapyramidal system	Prolongations of phonemes, intervals, unsteady rate, loudness
3. Tremors	Organic voice tremor	Extrapyramidal system	Rhythmic alterations in pitch, loudness, voice stoppages
Mixed	ALS	Multiple motor systems	Grossly defective articulation; extremely slow, laborious rate; marked hypernasality; severe harshness, strained or strangled voice; nearly complete disruption of prosody
	Wilson's disease		Reduced stress; monopitch; monoloudness; similar to hypokinetic dysarthria except no short rushes of speech
	MS		Impaired control of loudness; harshness

Adapted from Johns DF, ed. *Clinical Management of Neurogenic Communicative Disorders*. 2nd ed. Boston, MA: Little Brown, 1985, with permission.

B. Spastic dysarthria, as seen in pseudobulbar palsy, results from damage to the upper motor neuron (UMN) pathways in the frontal cortex, subcortical regions, or brainstem. Speech is shallow and labored with imprecise articulation. Pitch is low with a strained vocal quality, and hypernasality can be considerable. Dysphagia may be documented as well. In addition to spastic dysarthria, the patient with pseudobulbar palsy may often exhibit emotional lability that may exhibit spontaneous outbursts of laughter or crying known as "pseudobulbar affect." Spastic dysarthria may also result from ischemic insults. Isolated or "pure" dysarthria results mainly from lacunar infarcts involving the internal capsule or corona radiata. Isolated dysarthria and facial paresis are considered a variant of the dysarthria-clumsy hand lacunar syndrome. Occasionally, an isolated lacune will interrupt the corticolingual fibers from the motor cortex, causing dysarthria but without hemiparesis. Other common causes of spastic dysarthria include traumatic brain injury, spastic cerebral palsy, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS).

C. Mixed dysarthria is caused by simultaneous damage to two or more primary motor components of the nervous system, such as combined UMN and lower motor neuron (LMN) lesions. This form of dysarthria is common in patients with MS, ALS, or severe traumatic brain injury. The patients may speak with very slowly and with great effort. Articulation is markedly impaired with considerable hypernasality. Pitch continues to be low with a strained or strangled vocal quality. Prosody is completely disrupted with intonation errors and inappropriately shortened phrases/sentences. Bulbar involvement in ALS often presents in this fashion with dysarthria, hypophonia, drooling of saliva, and progressive swallowing difficulties (Fig. 19.1).

D. Ataxic dysarthria is usually associated with cerebellar disorders. Patients present with decreased motor coordination for accurate articulation with abnormal speech rhythm and syllable repetition. Likewise, patients are unable to accurately complete dysdiadochokinetic tasks with variations in pitch and loudness. Prosody impairment is characterized by prolonged intervals between syllables or words with excess stress on certain syllables and words. Ataxic dysarthria is caused by damage to the cerebellum or cerebellar connections to other parts of the brain. Isolated cerebellar dysarthria has also been reported with small infarcts in the left paravermian zone of the ventral cerebellum (lobulus simplex and semilunaris superior).

E. Hypokinetic dysarthria, most typically seen in parkinsonism, is associated with hypophonia or reduced vocal loudness, in addition to monotonous speech with a slow and flat rhythm. Initiation of speech is difficult, resulting in inappropriate silences intermixed, however, with short rushes of speech. The rate is variable with wide fluctuations in pitch.

F. Hyperkinetic dysarthria also occurs secondary to damage to the basal ganglionic pathways and is typified Huntington's disease. Damage to this system causes involuntary movements

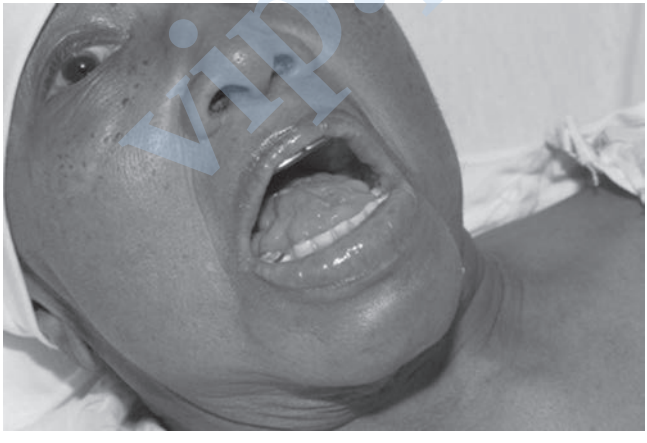


FIGURE 19.1 Diffuse tongue atrophy and fasciculations in a patient with bulbar MND.

such as tremors, dyskinesias, athetosis, and dystonia. Vocal quality may be described as harsh, strained, or strangled and is often associated with spasmodic dysphonia.

IV. DIFFERENTIAL DIAGNOSIS

The major clinical distinctions are between dysarthric, dysphonic, apraxic, and aphasic disorders. Both dysarthria and apraxia are considered to be motor speech disorders, and it may be sometimes difficult to differentiate among them. Apraxia of speech is a motor programming or planning disorder involving speech production tasks. Automatic and involuntary tasks are usually spared. Errors in articulation are inconsistent with primarily vowel and consonant distortions. Initiation is very difficult with obvious effortful grouping in an attempt to achieve accurate movement of the articulators. Patients are often aware of the errors and make attempts at correcting them. However, they are often unsuccessful in achieving initial articulatory configurations or transitioning from one sound to the next.

Aphasia is a loss or impairment of language processing caused by brain damage (see Chapter 3), whereas dysarthria is a problem in speech articulation. It is not uncommon for aphasia and dysarthria to coexist. A person with aphasia may be able to communicate with adequate breath support, voicing, and articulation, but may be unable to comprehend others or name, repeat, or express themselves adequately. Patients may also have isolated anomia (word finding difficulty) with inability to state certain words or name specific persons or objects.

Dysphonia is a term used to describe hoarseness or other phonation disorders. It is a characteristic of certain types of dysarthria; however, it may stand alone when describing other voice disorders. Spasmodic dysphonia is a neurological voice disorder that involves involuntary tightening or constriction of the vocal cords, causing interruptions of speech and affecting the voice quality, which can be strained or strangled. Voice overuse, illness, trauma, and stress can also result in chronic spasm, paresis, or vocal cord paralysis. Laryngitis and gastroesophageal reflux are common non-neurologic causes of chronic hoarseness.

V. DIAGNOSTIC EVALUATION

A detailed history and thorough neurological examination are necessary to determine the possible underlying etiology of the different types of dysarthria. The presenting symptoms, duration, pattern of speech disturbance, and progression of symptoms may help elucidate the mechanism of dysarthria. Other neurologic symptoms, medical comorbidities, and knowledge of contributory medications or exposures may also help determine the etiology of the dysarthria. For example, patients with extrapyramidal disorders have slow, quiet, and monotonous speech, which is gradually progressive and is associated with slowness of movement, falls, and tremors. Scanning speech with dysprosody is suggestive of a cerebellar disorder, especially when lack of coordination and gait unsteadiness are present. Patients with an LMN lesion may have pronounced tongue atrophy and fasciculations, with gradual and progressive muscle weakness, whereas an UMN disease is characterized by spastic and explosive speech. Palatal palsy and decreased gag reflex with tongue weakness may indicate bulbar involvement, whereas a brisk jaw jerk, hyperactive gag reflex, and emotional lability are suggestive of pseudobulbar palsy. Mechanical factors contributing to dysarthria including pharyngeal, vocal cord, tracheal, and other airway lesions including trauma and masses in these areas must also be considered.

Neuroimaging studies of the head or neck are helpful in diagnosing central and peripheral causes (see Chapter 32) with MRI with contrast enhancement as the preferred modality. Electromyography (EMG) and nerve conduction studies are an important tool in the diagnosis of MND, peripheral nerve injury or focal dystonia, polyneuropathy, myopathy, or neuromuscular junction disorders such as myasthenia gravis or the Lambert–Eaton myasthenic syndrome (see Chapter 33). Repetitive nerve stimulation or single fiber EMG to help diagnose neuromuscular junction syndromes should be done (when indicated). Lumbar

puncture and CSF analysis are discussed in Chapter 33. Other tests include pulmonary function studies and certain blood tests that may be specific to the diagnostic possibilities producing dysarthria including blood tests to assess for inflammatory or infectious causes, genetic diseases, or acquired and autoimmune disorders.

VI. EVALUATION BY A SPEECH–LANGUAGE PATHOLOGIST

In the evaluation of speech disorders, a speech–language pathologist (SLP) is often consulted to differentiate among the various types of dysarthria and help determine the best treatment strategies. Several core components are included in the evaluation. The SLP, after reviewing the neurological and medical evaluation, conducts an interview with either the patient and/or the closest relative. This interview helps to further define the time of onset, pattern of symptoms, previous assessments completed or treatment received, and the course of symptom improvement of the dysarthric disorder over time. An examination of the physical structures of the speech mechanism, as well as an assessment of articulation, respiration, phonation, resonance, and prosody is then performed. This includes a thorough oral mechanism examination assess strength, rate of movement, range of motion, and coordination of the speech mechanism including the jaw, lips, tongue, and velopharyngeal function. Deviations from the norm give way to articulation errors. Articulation can further be assessed in dysdiadochokinetic tasks and by listening to a brief speech sample. Abnormalities are noted with the production of imprecise consonants, producing voiced for voiceless syllables, repeated or prolonged phonemes, or vowel distortions. Speech intelligibility can be rated as well. Examples of improperly voiced syllables are "BAT for PAT; DIME for TIME; GOAT for COAT."

With decrease in laryngeal control, a patient may be unable to produce voiceless syllables. Abnormalities in respiration are often observed in sustained phonation tasks. A patient may be unable to sustain a vowel, such as "ah," with normal loudness for a period of time (approximately 5 seconds). Verbal output may also be limited to single words or short phrases due to a lack of expiratory effort. Vocal quality may be breathy, and a patient may be unable to maintain voicing throughout the length of a phrase or sentence. Voicing may start strong, but gradually fade with increased phrase or sentence length.

Appropriate phonation is very dependent on adequate respiration. Adequate breath support is required to achieve functional vocal fold closure in order to produce a sound. Abnormalities in voicing may be attributed to unilateral or bilateral vocal fold paralysis, a vocal cord mass, or vocal cord edema. Vocal fold adduction may be compromised resulting in a breathy vocal quality (hypofunction). Excessive adduction of the vocal folds gives way to possible strained or strangled output in addition to increased pitch (hyperfunction). If there is a suspicion of an abnormal approximation of the vocal folds, a consultation by an otolaryngologist (ENT) may be recommended. Assessment of phonation by an SLP includes sustained phonation tasks. Having the patient sustain a vowel ("ah" or "ee") for as long as they can allows the SLP to discriminate between variations in pitch, breath support, loudness, and voice quality. Of note, measuring maximum length of phonation provides limited direction in differentiating among dysarthrias because sustained phonation is not characteristic of functional conversational speech.

Hypernasality and hyponasality are characterized by abnormalities in resonance. Hypernasality may be evidenced by an excess escape of air into the nasal cavity resulting from reduced velopharyngeal closure or soft palate weakness. It is also important to watch the soft palate at rest, and during sustained phonation, for functional movement or possible fatigue. Hyponasality results from inadequate velopharyngeal opening, which may be caused from a complete or partial blockage of nasal airway. If a blockage is suspected, further ENT evaluation may be required. Prosody can be analyzed by assessing the coordination of respiration, phonation, and articulation. Errors in prosody may present as abnormally slowed or rapid rate of speech, decreased stress or emphasis patterns, intonation errors, or inappropriately shortened phrases/sentences that can be mixed with intervals of silence. Prosody can be assessed within the speech sample or by having the patient imitate various phrases. One sample of stress or intonation variations is: "Is THAT your car?" "Is that YOUR car?"

"Is that your CAR?" Clearly, varying the stress/intonation within this short sentence may result in significant changes in the meaning of a sentence.

Impairments to any of the above listed speech mechanisms resulting in dysarthria often coexist with dysphagia. Current standards require that a swallow screening be documented on all stroke patients; however, this should not exclude screening for dysphagia in any of the other disorders when examining dysarthria. If there are noted dysphagic symptoms with a brief swallow screening, a formal swallow evaluation is needed including a thorough history for possible dysphagic symptoms and assessment of oral mechanisms for strength, movement, and coordination of the muscles for swallowing. If then deemed safe, the patient is given various consistencies of liquids and/or solids, and tolerance is observed. The SLP, through observation and hands-on assessment, notes oral, pharyngeal, and sometimes esophageal difficulties. Depending upon the clinical results of the bedside exam, the SLP may recommend oral feeding with the least restrictive liquids and/or solids, a video fluoroscopic swallow evaluation, or both. When indicated, a fiberoptic laryngoscopic examination may also be helpful for the assessment of swallowing function as well as actual movement of the vocal cords and tracheopharygneal muscles involved in the mechanics of swallowing and speech production.

VII. MANAGEMENT

The underlying etiology of the dysarthria and prognosis for improvement must be taken into consideration when devising a treatment plan. Treatment includes patient and family education and training in compensatory strategies. Treatment of respiratory/phonatory deficits may include improving breath support to increase vocal volume. Slowing the rate of speech may be necessary to improve articulation and intelligibility. Non-speech oral motor training may be recommended for strengthening muscles and increasing mouth, tongue, and lip range of motion and movement. Changes in loudness and prosody, through intonation and stress patterning tasks, may be targets of intervention as well. In severe cases, augmentative and alternative communication strategies, such as computerized voice production systems, may be needed.

Recommended Readings

Amarenco P, Cherrie-Muller C, Roullet E, Bousser MG. Paravermal infarct and isolated cerebellar dysarthria. *Ann Neurol*. 1991;30(2):211–213.

Biller J, Gruener G, Brazis P. *DeMyer's The Neurologic Examination. A Programmed Text*. 6th ed. New York, NY: McGraw Hill Medical; 2011.

Brazis PW, Masdeu JC, Biller J. The localization of lesions affecting cranial nerve XII. In: *Localization in Clinical Neurology.* 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins, Wolters Kluwer; 2011:377–383.

Clebisoy M, Tokucoglu F, Basoglu M. Isolated dysarthria—facial paresis syndrome: a rare clinical entity which is usually overlooked. *Neurol India*. 2005;53(2):183–185.

Darley FL, Aronson AE, Brown JR. *Motor Speech Disorders.* Philadelphia, PA: W. B. Saunders; 1975.

Duffy JR. *Motor Speech Disorders: Substrates, Differential Diagnosis, and Management.* St. Louis, MO: Mosby; 1995.

Dworkin JP. *Motor Speech Disorders: A Treatment Guide.* St. Louis, MO: Mosby; 1991.

Hustad KC, Beukelman DR, Yorkston KM. Functional outcome assessment in dysarthria. *Semin Speech Lang.* 1998;19:291–302.

Hustad KC, Jones T, Dailey S. Implementing speech supplementation strategies: effects on intelligibility and speech rate of individuals with chronic severe dysarthria. *J Speech Lang Hear Res.* 2003;46:462–474.

Kaye M. *Guide to Dysarthria Management: A Client–Clinician Approach.* Eau Claire, WI: Thinking Publications; 2005.

Kent RD, Duffy JR, Slama A, Kent JF, Clift A. Clinicoanatomic studies in dysarthria: review, critique, and directions for research. *J Speech Lang Hear Res.* 2001;44:535–551.

Kuncl RN, ed. *Motor Neuron Disease*. London, UK: W.-B. Saunders; 2002.

Love RJ, Webb WG. *Neurology for the Speech–Language Pathologist*. 2nd ed. Boston, MA: Butterworth–Heineman; 1992.

Mosby's Medical Dictionary. Elsevier/Mosby; 2010

Murdoch B. *Dysarthria: A Physiological Approach to Assessment and Treatment*. Frederick, CO: Aspen Publishers; 1998.

Okuda B, Kawabata K, Tachibana H, Sugita M. Cerebral blood flow in pure dysarthria. Role of frontal cortical hypoperfusion. *Stroke*. 1999;30:109–113.

Okuda B, Tachibana H. Isolated dysarthria. *J Neurol Neurosurg Psychiatry.* 2000;68:119–120.
Pinto S, Ozsancak C, Tripoliti E, Thobois S, Limousin-Dowsey P, Auzou P. Treatments for dysarthria in Parkinson's disease. *Lancet Neurol.* 2004;3:547–556.
Robert D, Bianco-Blache A, Spezza C, Verschueren A, Pouget J, Giovanni A. Assessment of dysarthria and dysphagia in ALS patients. *Rev Neurol* (Paris). 2006;162:445–553.
Robin DA, Yorkston KM, Beukelman DR. *Disorders of Motor Speech*. Baltimore, MD: Paul H. Brookes Publishing; 1996.
Ropper AH, Samuels MA. Adams and Victor's. Principles of Neurology. Ninth Edition. Disorders of speech and language. New York, NY: McGraw-Hill; 2009: Ch23, 461-479.
Sellars C, Hughes T, Langhorne P. Speech and language therapy for dysarthria due to non-progressive brain damage. *Cochrane Database Syst Rev.* 2005;3.
Urban PP, Wicht S, Vukurevic G, et al. Dysarthria in acute ischemic stroke. Lesion topography, clinicoradiologic correlation, and etiology. *Neurology*. 2001;56:1021–1027.
Vogel D, Cannito MP. *Treating Disordered Speech Motor Control.* 2nd ed. Austin, TX: Pro-Ed; 2001.
Yorkston KM, Beukelman DR, Strand EA, Bell KR. *Management of Motor Speech—Disorders in Children and Adults.* 2nd ed. Austin, TX: Pro-Ed; 1999.

CHAPTER

20 Approach to the Patient with Acute Headache

David Lee Gordon

Acute headache is a common chief complaint in the emergency department. **Primary headache,** such as migraine and cluster, is a condition in which headache is a primary manifestation and no underlying disease process is present. **Secondary headache** is a condition in which headache is a secondary manifestation of an underlying disease process. Most patients with acute headache have primary headache, particularly migraine. Performing an expensive battery of tests on all patients with acute headache is neither cost-effective nor appropriate. Failure to perform diagnostic tests in certain patients with acute headache, however, will result in failure to detect life-threatening, yet treatable, causes. The challenge to the clinician in the emergency setting is not to be lulled to sleep by the frequent migraine attacks and to remain vigilant for the other causes of acute headache.

Migraine is so common that many patients with a secondary headache have a history of migraine, making diagnosis in the acute setting quite difficult. Certain clues in the history and examination should lead to the performance of a diagnostic evaluation in search of the cause of secondary headache. The primary goals of the clinician treating a patient with acute headache are 3-fold: (1) diagnose the cause of headache, (2) provide emergency therapy, and (3) provide the patient with a means of long-term care. These goals apply for patients with primary or secondary headache. Primary headaches are chronic conditions that manifest as multiple acute attacks. Secondary headaches generally are caused by diseases that necessitate both urgent and prolonged care. This chapter deals with the diagnosis of acute headache. The diagnosis of chronic headache and therapy for conditions that cause headache are dealt with elsewhere in Chapter 21.

I. PATHOPHYSIOLOGY

The pathophysiology of head pain is likely the same no matter its cause. Among patients with brain tumor, patients with a past history of primary headache are more likely to have a tumor-related headache than those without a history of primary headache. Thus, the description of head pain alone is not a reliable predictor of whether a headache is primary or secondary. Hemicranial throbbing pain is not always a feature of migraine and can be a feature of intracranial disease. Dull aching head pain occurs in patients with primary headache and patients with brain tumors. Although current understanding of the cause of head pain is not complete, a plausible explanation of the pathophysiologic mechanism of headache that emphasizes the common final pathway of primary and secondary headaches is depicted in Figure 20.1. The schema provides an explanation for the "migrainous" characteristics of some secondary headaches.

II. HISTORY

A. A **history of headaches,** especially the relation of past headaches to the current headache, is the most important information needed to determine whether a diagnostic evaluation is necessary. A history of similar headaches for many years suggests a primary headache disorder. If, on the other hand, this headache is **different** in character from past headaches and especially if this is the **first** headache of the patient's life, if this is the **worst** headache that the patient has had, or if the pain is **persistent** despite the use of measures that relieved previous headaches, a secondary headache is more likely

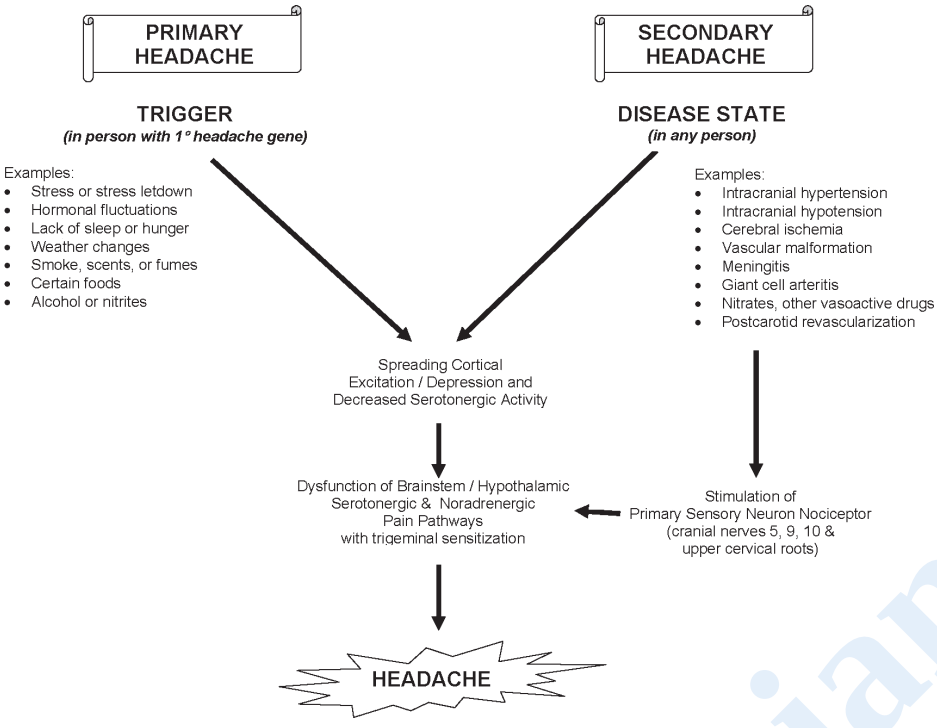


FIGURE 20.1 Plausible schema for pathophysiologic mechanism of headache depicts the common final pathway of primary and secondary headaches.

TABLE 20.1 Clinical Features Suggestive of Secondary Headache

Headache features
Different headache
First headache
Worst headache
Persistent headache
Exacerbation by head position
Onset
With Valsalva's maneuver
With head trauma
After 50 years of age
Associated features
Focal neurologic signs (abnormal examination findings)
Change in consciousness
Fever
Seizure
Nuchal rigidity
Papilledema
Preretinal or retinal hemorrhages
History of
Bleeding diathesis
Hypercoagulable state
Cancer
Risk factors for HIV infection or AIDS

(Table 20.1). If the patient has had similar headaches for only a few months, weeks, or days, then the possibility of secondary headache increases, and further investigation is warranted. Although it is common for the character of primary headache disorders to change throughout a lifetime, if the current headache differs from previous headaches, the clinician is obligated to investigate.

B. Age at onset of primary headache disorders is generally childhood to young adulthood. An age at onset older than 50 years is particularly suggestive of secondary headache.

C. Activity at onset of headache may suggest cause of headache. Although Valsalva's maneuver, change in position, or head trauma can precipitate or exacerbate migraine, the presence of any of these features should raise the suspicion of secondary headache.

1. **Valsalva's maneuver** may precipitate aneurysmal rupture and resultant subarachnoid hemorrhage (SAH). It can also precipitate or exacerbate a CSF leak and result in headache due to intracranial hypotension. Headache during coitus can occur as a result of aneurysmal rupture or as a result of coital migraine. The first time a person experiences coital headache, he or she needs a complete evaluation to rule out aneurysmal SAH.
2. **Changes in position** exacerbate several types of headache. Headaches worse in the supine position suggest increased intracranial pressure (ICP), for example, due to intracranial mass lesion, hydrocephalus, or cerebral venous thrombosis (CVT). Headaches worse when upright (and improved when supine) suggest decreased ICP due to a CSF leak. "Low-CSF-pressure headaches" are especially common after lumbar puncture (LP) but may occur spontaneously or after Valsalva's maneuver. Mobile intraventricular tumors, such as third-ventricle colloid cyst, may cause intermittent hydrocephalus and headaches that occur only in a particular head position.
3. **Head trauma** can result in subdural hematoma but may also trigger migraines.
4. **Exercise** can precipitate migraine or another type of primary headache that is sensitive to indomethacin.

D. The **characteristics of a headache** are most helpful in determining whether the current headache is different from previous headaches experienced by the patient. Certain characteristics are suggestive of but not pathognomonic for certain causes of headache.

1. **Severity** of pain is important in that any patient who says he or she has "the worst headache of my life" needs an urgent and complete evaluation, with SAH highest in the differential diagnosis. Both primary headaches and secondary headaches, however, can manifest as very severe or very mild pain.
2. The **time frame** of onset of pain is more discriminating. Very rapid onset of headache suggests a sudden increase in ICP, particularly due to SAH. Mass lesions such as tumors, abscesses, and subacute or chronic subdural hematoma usually manifest gradually over days to months. Gradual onset of headache over minutes to hours is consistent with migraine. The headache of giant cell (temporal) arteritis tends to be subacute to chronic in presentation.
3. **Duration** of primary headaches is variable, although they typically last hours to days. Headaches that persist for longer periods despite treatment are worrisome and suggestive of secondary headache.
4. **Location** of headache and radiation of pain are nonspecific. Many posterior lesions cause frontal headache. Both primary and secondary headaches can be unilateral or bilateral. The pain of both migraine headaches and secondary headaches can radiate.
5. **Quality** of headache is nondiscriminating. Despite the traditional teaching that migraines must be pounding or throbbing, they are just as often pressure-like, squeezing, sharp, stabbing, or dull. Cluster headaches typically are described as boring, sharp, or lancinating, but so might the headaches associated with other pathologic processes.
6. **Associated symptoms** of the headache can offer important clues to the cause of headache (Table 20.1).
   a. **Nausea and vomiting** are common features of migraine, but their presence in a person with new or sudden headache is worrisome because they suggest increased ICP or a posterior fossa lesion.
   b. **Photophobia and phonophobia** can be part of migraine or a meningeal process such as SAH or meningitis.
   c. **Neck stiffness** (anteroposterior nuchal rigidity) is typical of a meningeal process.

d. **Change in consciousness** rarely occurs in migraine, but its presence should alert the clinician to more serious causes of headache.

e. **Focal neurologic symptoms** (e.g., aphasia, visual symptoms, vertigo, ataxia, hemiparesis, or hemisensory deficit) can occur suddenly in association with headache in patients with stroke, seizure, subdural hematoma, and migraine. In this case, migraine is a diagnosis of exclusion, and the clinician is obliged to investigate for underlying disease. Transient ischemic attacks (TIAs) typically last 5 to 20 minutes. Stroke and subdural hematoma symptoms persist. Todd's paralysis of partial seizures and the aura of migraine often last hours. Focal symptoms of ischemia or hemorrhage typically are "negative" and "static" (e.g., hemibody sensory loss), whereas focal symptoms of migraine typically are "positive" and "migratory" over minutes to hours (e.g., tingling in fingertips progressing to involve the ipsilateral hemibody). Partial seizures can result in symptoms that travel over seconds. Headache in a person older than 50 years with monocular blurred vision and a swollen optic disc suggests the anterior ischemic optic neuropathy (AION) of giant cell arteritis. Binocular visual symptoms can be migrainous or due to occipital pathologic conditions. Certain visual symptoms are classic for migraine, such as scintillating scotomata (blind areas surrounded by sparkling zigzag lines), photopsia (unformed flashes of light), and fortification spectra (slowly enlarging, sparkling, and serrated arcs).

f. **Fever, diaphoresis, chills, or rigors** suggest infection. Fever of any cause or generalized infection can cause headache, but if headache, neck stiffness, or decreased consciousness is a prominent symptom, meningitis is highest in the differential diagnosis.

E. Family history of headache is important yet extremely difficult to obtain when a patient has prominent pain, nausea, or cognitive dysfunction as can occur with either primary or secondary headache. Even if the patient is coherent or a relative is available, persons often are not aware of a family history of headache. Migraines tend to be most prominent in early adulthood, when children are too young to realize their parent has headaches, and the patient no longer lives under the same roof with parents or siblings. In addition, rationalization of relatives regarding the cause of headaches (e.g., "sinus" or "tension") is usually believed by the patient, making a family history of "migraine" difficult to obtain.

III. PHYSICAL EXAMINATION

Physical examination may demonstrate signs of a disease that causes secondary headache. A detailed neurologic examination is particularly important; any subtle abnormality should be enough to stimulate a diagnostic evaluation (Table 20.1).

A. General examination.

1. **Vital signs.** Fever suggests an infectious cause of headache. The presence of arterial hypertension in a patient with headache is common but is rarely causative. Hypertension occurs as a result of migraine attacks, cerebral ischemia, and intracranial hemorrhage.
2. **General appearance.** Cachexia may be present among patients with chronic diseases such as cancer, AIDS, tuberculosis, and sarcoidosis. Headache due to tumor, abscess, granuloma, or meningitis may be the presenting symptom among such patients.
3. **Head.** Evidence of cranial trauma includes face and scalp abrasions and contusions and signs of skull fracture—depressed section of skull, Battle's sign (postauricular ecchymosis), raccoon sign (periorbital ecchymosis), hemotympanum, CSF otorrhea, and CSF rhinorrhea. Skull tenderness to palpation can occur as a result of subdural hematoma. Poor dentition or dental abscesses may result in intracranial abscess. Although tenderness to palpation over the frontal sinus or maxillary sinus may suggest infection of these structures, migraine frequently results in external carotid territory vasodilatation with resultant sinus "fullness," "pressure," and tenderness. The presence of fever and purulent discharge from the sinuses is more helpful in diagnosing sinusitis. Tenderness to palpation over the mastoid process suggests mastoiditis, a possible precursor to CVT. Otoscopic examination may show ear infection as well as hemotympanum or otorrhea.

Temporal tenderness or diminished temporal artery pulses in a person older than 50 years are consistent with giant cell arteritis. Auscultation of the skull may demonstrate cranial bruits that occur as a result of arteriovenous malformation (AVM).

4. **Neck.** Meningeal signs include anteroposterior nuchal rigidity, Kernig's sign (inability to extend the knee after passive hip flexion in the supine position), and Brudzinski's sign (involuntary hip flexion after passive flexion of the neck in the supine position) and imply the presence of meningitis or SAH. Evidence of neck trauma includes pain on lateral neck movement and neck immobility.
5. **Skin.** A petechial rash over the axillae, wrists, and ankles is consistent with meningitis due to meningococcus. Skin examination may reveal bruising suggestive of a bleeding diathesis, splinter hemorrhages of distal digits suggestive of cardioembolism, or lesions suggestive of a neurocutaneous disorder such as neurofibromatosis, tuberous sclerosis complex, or cutaneous angiomatosis; these conditions are associated with intracranial lesions that may cause headache. Melanoma suggests the possibility of cerebral metastasis causing headache. Lesions of Kaposi's sarcoma are consistent with AIDS, which is associated with several intracranial diseases that cause headache.
6. **Lymph nodes.** Lymphadenopathy occurs among patients with cancer, AIDS, chronic infections, or chronic inflammatory diseases. The possible presence of any of these conditions should stimulate evaluation for a cause of secondary headache.

B. **Neurologic examination.** The neurologic findings are normal in patients with primary headache. A change in consciousness or focal deficit raises the possibility of secondary headache. The funduscopic examination may reveal papilledema in patients with ICP, AION in patients with giant cell arteritis, or preretinal hemorrhage in patients with intracranial hemorrhage. Headache in association with either partial third nerve palsy or complete but pupil-sparing third nerve palsy is worrisome because it suggests posterior communicating artery aneurysm. A patient with these findings needs urgent cerebral angiography—via catheter or computed tomography (CTA). The combination of proptosis, oculomotor findings, and headache suggests disease in the orbit, superior orbital fissure, or cavernous sinus; evaluation should be urgent. Acute glaucoma can manifest as headache, especially periorbitally. An injected conjunctiva and a hard globe are consistent with the diagnosis. Horner's syndrome can occur in isolation ipsilateral to a carotid artery dissection.

IV. LABORATORY STUDIES

Laboratory studies are necessary in the evaluation of any patient believed to have a secondary headache (Fig. 20.2). There are no laboratories that identify primary headache.

A. **Blood evaluation.**

1. **Complete blood cell count.** Leukocytosis is consistent with infection, and marked leukocytosis is found in leukemia, which can cause headache through carcinomatous meningitis or cerebral venous occlusion. Leukopenia is found in AIDS. Anemia can occur in patients with cancer or giant cell arteritis. It also can be associated with a low-flow state that precipitates CVT. Essential thrombocythemia is a hypercoagulable state that can cause arterial or venous occlusions in the brain with resultant headache.
2. **Chemistries.** Renal failure can be associated with headache. Both renal function and liver enzyme abnormalities have implications regarding past drug use and options for future medical management. In general, however, abnormalities in serum chemistries may provide clues to a generalized, underlying disease process that can cause headache.
3. **Erythrocyte sedimentation rate (ESR)** and **C-reactive protein (CRP)** are the initial tests to perform if giant cell arteritis is suspected. Moderate elevations in ESR (up to 50 mm per hour) are common among healthy elderly patients. Both ESR and CRP are nonspecific; elevations can be present in patients with infection, inflammatory disease, or cancer. Still, marked elevations of ESR or any elevation of CRP in a patient older than 50 years with new-onset headache should prompt administration of high-dose steroids and temporal artery biopsy.

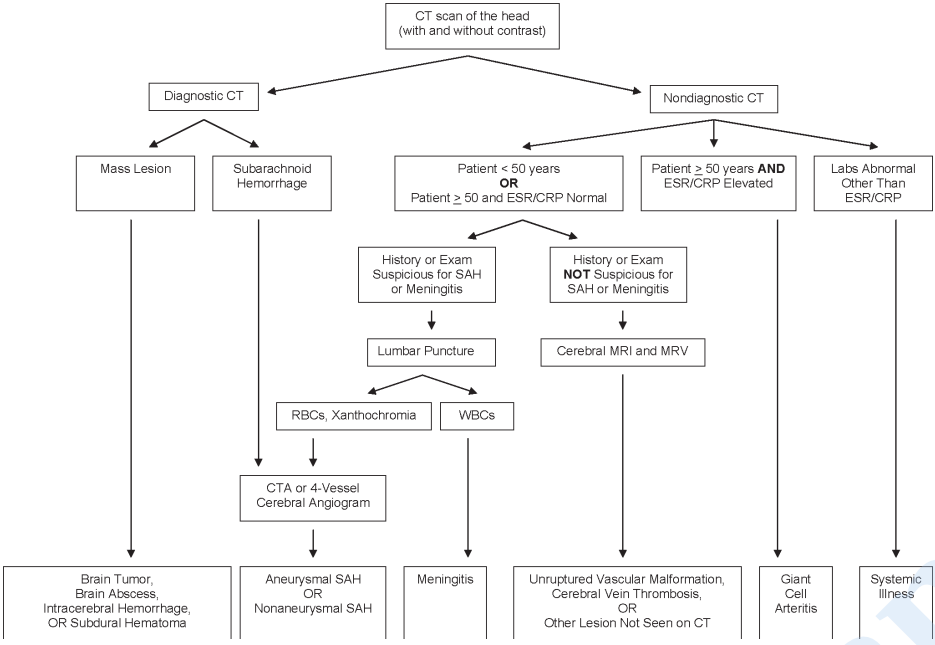


FIGURE 20.2 Diagnostic algorithm for a patient with suspected acute secondary headache.

4. **Prothrombin time** and activated **partial thromboplastin time** may provide evidence of a bleeding diathesis that results in intracranial hemorrhage and headache.
5. **Thyroid function tests.** Thyroid disease can cause headache by serving as a trigger in a migraine patient or can cause headache by other mechanisms.
6. **Hypercoagulable profile** is indicated for patients with suspected CVT and for patients younger than 50 years with suspected ischemic stroke or TIA.
7. **Arterial blood gas.** Hypoxia can cause headache; arterial blood gas measurement should be performed if clinically indicated.
8. **Drug screen.** Use of sympathomimetic drugs such as cocaine and amphetamines can be associated with intracranial hemorrhage or cerebral ischemia and resultant headache. Salicylate toxicity can result in diffuse cerebral edema with headache worsening. The excessive use of analgesics, whether over-the-counter or narcotic, can cause medication-overuse (i.e., analgesic rebound) headache and interfere with acute headache management.

B. Urine evaluation may reveal nephrotic syndrome (which can be associated with a hypercoagulable state and resultant CVT), infection (organisms and WBCs), evidence of peripheral embolization (RBC casts), or use of illicit or analgesic drugs.

C. Radiography. A chest radiograph may reveal hilar adenopathy or pulmonary lesions that provide clues regarding the identity of intracranial lesions that cause headache. Radiographs of the cervical spine may reveal evidence of neck trauma.

D. A **CT scan** is a preferred initial cerebral imaging study because of convenience, ability to detect bony changes in head trauma, and sensitivity in the detection of acute blood. Noncontrast scanning is mandatory because both contrast material and blood present because of acute bleeding are white (hyperdense) on CT scans. If only a contrast scan is obtained, there may be confusion about whether a lesion is hemorrhage or an enhancing mass. With time, blood becomes increasingly dark on CT scans. Consequently, subacute (2 to 14 days) subdural hematoma is isodense with parenchyma on CT scans and may be difficult to detect. MRI is better in the detection of subacute bleeding. The odds of detecting SAH with CT decrease with time from the onset of symptoms. Within a few days, a large percentage of CT scans are normal. Even in the acute phase, at least

5% of patients with SAH have normal CT scans. For any patient with suspected SAH, if the CT findings are normal, the clinician is obliged to perform a LP. Once noncontrast CT is performed, if a mass lesion is suspected, a contrast scan should be obtained. Mass lesions such as tumors and abscesses disrupt the blood–brain barrier and cause seepage of contrast medium around or in the lesion. A mass lesion can be isodense with parenchyma on noncontrast CT scans and therefore difficult to detect. Contrast scanning greatly increases the chance of detecting such a lesion.

E. **MRI** is usually a secondary cerebral imaging procedure in the evaluation of acute headache due to inconvenience and a perception that it is unable to detect acute blood. With the advent of T2*-weighted imaging, however, MRI is now equivalent to CT in the detection of acute blood. Furthermore, it is superior to CT in the detection of subacute blood and is especially useful in examinations of patients with suspected subacute subdural hematoma. MRI is superior to CT and even angiography in the detection of vascular malformations. Any patient with suspected unruptured AVM as a cause of headache needs MRI. MRI is superior to CT in the detection of parenchymal lesions and the visualization of the posterior fossa and inferior temporal lobes. Unlike CT, MRI provides information regarding blood flow in cerebral vessels. MRI is the procedure of choice in examinations of patients with suspected CVT. It depicts both parenchymal and venous abnormalities and leads to a correct diagnosis of this condition approximately 75% of the time. In patients with intracranial hypotension and low-pressure headaches, MRI may demonstrate diffuse thickening of the pachymeninges with gadolinium enhancement, engorgement of venous sinuses, or subdural fluid collections.

F. **Magnetic resonance angiography (MRA)** is indicated in the evaluation of patients with suspected CVT who do not undergo conventional angiography. An MRA offers a noninvasive way of evaluating the cerebral vessels. In general, contrast medium is not necessary. It, however, can mislead the clinician if not performed and interpreted properly—vessels with abnormal flow are not depicted, slow flow can mimic occlusion, and subacute thrombus can mimic normal flow. Acquisition of images should be perpendicular to flow to avoid in-plane flow artifact. Selective **MR venography (MRV)** is performed by means of saturating arterial inflow.

G. **LP.**

1. **Indications.** LP for CSF analysis is indicated if one suspects acute or chronic meningitis, SAH, pseudotumor cerebri, or low-CSF-pressure headache.
2. **Timing in relation to CT.** It is preferable to perform CT before LP. If CT shows significant mass effect such as shift across the midline, obliterated basilar cisterns, or a compressed fourth ventricle, LP should be avoided to avoid precipitating uncal or central herniation of brain tissue through the foramen magnum. If CT shows SAH, LP is not necessary. If bacterial meningitis is suspected, antibiotics should be started on the way to CT, and LP performed after normal CT findings are obtained. If CT is to be delayed for hours and one suspects bacterial meningitis, it is necessary to treat the patient with appropriate antibiotics (and dexamethasone) even before CT and LP. The prognosis among patients with meningitis is heavily influenced by promptness of treatment.
3. **CSF analysis.** Opening pressure is most important in patients with suspected pseudotumor cerebri (generally >250 mm Hg) or low-CSF-pressure headaches. If SAH is suspected, one should obtain cell counts in the first and last tubes of CSF and test for xanthochromia. Knowing that the number of RBCs does not change significantly between the two tubes helps to confirm the diagnosis and avoids the common dilemma of determining whether or not a bloody tap is "traumatic." Xanthochromia is the yellowish color of CSF supernatant that occurs because of either the presence of hemoglobin breakdown products or a very high-protein concentration. If the patient arrives for treatment days after a SAH, there may be no RBCs in the CSF, but xanthochromia due to hemoglobin breakdown persists for up to 2 weeks. Samples for culture of bacteria, fungus, and tuberculosis should be sent. Polymerase chain reaction is a sensitive means of determining the presence of infection. A Venereal Disease Research Laboratory test and cryptococcal antigen assessment should be performed as well. If cancer is suspected, at least 10 mL of fluid should be sent for cytologic analysis.

H. **Cerebral angiography (catheter or CTA)** should be performed urgently for any patient with evidence of SAH at CT or LP. A four-vessel arteriogram is mandatory

because predictions of aneurysm location based on CT findings are not always accurate, and many patients have multiple aneurysms. Delayed venous-phase images may detect CVT, which can cause subarachnoid bleeding.

I. **Electroencephalography** is indicated if seizures are being considered, as in the evaluation of a patient with headache and associated loss of consciousness. Headaches often occur in association with seizures. Partial seizures can result in transient neurologic deficits and can be difficult to differentiate from migraine with aura and TIA.

V. DIFFERENTIAL DIAGNOSIS

A. **Primary headache.**

1. **Migraine.**

a. **Definition.** Migraine is a genetic condition in which a person has a predisposition to episodic headaches, gastrointestinal dysfunction, or neurologic dysfunction. Severe headache need not be a feature of migraine. The International Headache Society's definition of migraine is quite specific for the purpose of research but is too limiting to be useful in clinical practice. Many investigators consider intermittent **tension-type headache** to be a form of migraine rather than a separate entity.

b. **Triggers.** A migraine attack occurs when a stimulus, or trigger, affects a person with the genetic predisposition to migraine. Examples of triggers are listed Figure 20.1. Women suffer more migraine attacks than do men because they are more frequently exposed to a trigger (estrogen level fluctuations of menstruation, pregnancy, oral contraceptives, and menopause), but they do not possess the gene more often than do men.

c. **Phases.** There are four main phases of migraine—prodrome, aura, pain, and postdrome. Not all phases need be present in any one migraine attack.

(1) The **prodrome** occurs hours to days before the headache and consists of mood changes (e.g., irritability and depression), excessive yawning, or food cravings (especially for chocolate, nuts, and bananas, mistakenly thought to be migraine triggers in the past).

(2) The **aura** can be visual, sensory, motor, or reflective of brainstem (e.g., vertigo and diplopia) or cerebral cortex (e.g., aphasia) involvement and occurs as a result of cortical spreading excitation and depression. As a consequence of the spreading chemical changes in the cortex, the symptoms typically migrate across the vision or body and progress from one type of symptom to another (e.g., floating or pulsating spots in the vision followed by hemibody tingling traveling down the body). The excitation phase leads to positive sensory symptoms such as photopsia and tingling. Visual symptoms can be any shape (spots, circles, wavy, or zigzag lines), any color (clear, silver, black, white, or brightly colored), and hemianopic or present throughout the visual field. An aura may be the only symptom of a migraine attack (aura without headache and acephalgic migraine); may occur before, during, or after the headache (headache with aura and classic migraine); or may not be present at all (headache without aura and common migraine).

(3) The **pain** of migraine may be in the head, abdomen, or chest. The headache characteristics are not as helpful in diagnosis as is generally believed. Not all migraine attaches are characterized by severe, throbbing, hemicranial headache. Migraine headaches may be mild, squeezing, dull, or bilateral. Typically, the headache onset is gradual over minutes to hours, and duration is hours to a few days. It may be associated with nausea, vomiting, photophobia, phonophobia, kinesiophobia, osmophobia, thermophobia, or difficulty concentrating. Gastrointestinal symptoms such as abdominal cramping, flatulence, and diarrhea may predominate during this phase ("abdominal migraine"). Chest pain may predominate during migraine attacks ("precordial migraine"). Transient dysautonomia often occurs during this phase and results in blood pressure changes, usually hypertension, but occasionally hypotension and the syndrome of "syncopal migraine."

(4) The **postdrome** is marked by malaise for several hours after the headache. Mood changes, impaired concentration, and scalp or muscle tenderness may also be present. Sleep often helps migraine attacks, and patients tend to crave rest in a dark, quiet room.

d. **Difficulties in migraine diagnosis.** Migraine is a purely historical diagnosis. Aided by folklore and advertising for over-the-counter medications, patients tend to believe their recurrent headaches are due to "sinus," "tension," or "regular" headache. It is often beneficial to educate the patient regarding migraine before obtaining a history. If there is any doubt in the clinician's mind regarding the diagnosis of migraine, a diagnostic evaluation is necessary to rule out other causes of headache.

2. **Cluster headache** is much less common than migraine. It occurs primarily among men and manifests as severe, stabbing, periorbital pain with associated ipsilateral tearing, injected conjunctiva, nasal congestion, and rhinorrhea. Alcohol often precipitates attacks. The attacks occur most frequently at night, last 30 minutes to 3 hours, and can occur several times per day. Unlike patients with migraine, patients with cluster headaches prefer to pace and keep active during the attacks. The term *cluster* refers to the seasonal occurrence of multiple episodes over weeks to months with intermittent periods of remission. There are episodic and chronic forms. Cluster headache is now considered to be one of the **trigeminal autonomic cephalalgias,** along with paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

B. Secondary headache.

1. **SAH** is the most important consideration in the evaluation of patients with a first or worst headache, yet it is frequently missed: 25% of patients with SAH are initially treated for another condition. Most patients with SAH have headache as the initial symptom. The headache is unilateral in 30% of patients, and findings at neurologic examination may be normal. Many patients (estimates range from 20% to 95%) have a milder sentinel headache that precedes the cataclysmic event. The clinician should consider the sentinel headache of SAH in the evaluation of patients with mild, yet different headaches. CT usually provides enough information for a diagnosis, but if SAH is suspected clinically and CT findings are normal, LP is mandatory. One should examine the CSF as described in IV.G. Once SAH is diagnosed with CT or LP, urgent CTA or four-vessel catheter angiography is required to identify aneurysms amenable to surgical clipping or coiling.
2. **Meningitis,** particularly bacterial and viral meningitis, often manifests as acute headache. Fever, neck stiffness, confusion, decreased consciousness, and cranial neuropathy may be present. Bacterial meningitis is fatal if the patient is not treated. Administration of broad-spectrum antibiotics should be started as soon as there is clinical suspicion—before CT and LP are performed. If one suspects bacterial meningitis, CSF analysis is mandatory. If CT can be performed within minutes, one should perform CT before LP to rule out mass effect. Section IV.G. describes steps to take if CT cannot be performed immediately. Antibiotic therapy can be adjusted once culture results are known.

   Aseptic meningitis and chronic meningitis can also manifest as acute, persistent headache. Cranial neuropathy and radiculopathy are more common, and neck stiffness is less common in chronic meningitis. Conditions associated with chronic meningitis include syphilis, fungal infection (especially cryptococcus), tuberculosis, sarcoidosis, Lyme's disease, cancer, and lymphoma. Any patient with AIDS who has a headache and normal findings at contrast CT of the brain needs LP in search of cryptococcal meningitis. Patients with suspected neoplastic meningitis may need several LPs for cytologic analysis of CSF before the diagnosis is confirmed.
3. **Subdural hematoma** occurs as a result of the tearing of bridging veins. When acute, it presents as a rapidly progressive neurologic deficit, but headache may be the only symptom of subacute or chronic subdural hematoma. Although subdural hematoma typically is caused by closed head trauma, in many cases a history of trauma is absent especially in older patients. CT usually provides enough information for the diagnosis, but blood from subacute bleeding (2 days to 2 weeks) is isodense with brain parenchyma on CT scans, making it difficult to detect. MRI is superior in the detection of subacute bleeding. **Epidural hematoma** caused by the rupture of a meningeal artery, often in

association with skull fracture, usually manifests as rapidly progressive neurologic deficit and decreased consciousness rather than as headache. The classic sequence of head trauma, brief loss of consciousness, lucid interval, and rapid progression to coma occurs in less than one-third of patients.

4. **Intracerebral hemorrhage** manifests as focal neurologic findings and usually a change in consciousness or cognition. Estimates of headache incidence with intracerebral hemorrhage vary depending on the size and location of the hemorrhage. Among patients who are able to communicate, headache is more common with larger hemorrhage and hemorrhage in the cerebellum and cortex (lobar hemorrhage). Cerebellar hemorrhage presents with acute posterior headache, nausea, vomiting, and inability to stand. CT provides enough information for the diagnosis, and emergency surgery may be lifesaving.
5. **Ischemic stroke and TIA** always manifest as focal neurologic deficit. Headache occurs in 15% to 20% of patients with acute cerebral ischemia. The presence of headache with acute cerebral ischemia suggests at least temporary ischemia of the large artery territory, even if only a subcortical "lacunar" infarct is seen on CT scans or MR images (not all small-artery "occlusions" are caused by small-artery "disease"). Despite traditional teaching, it is unclear whether headaches are more common in association with cardioembolic rather than atherosclerotic stroke. CT findings often are normal in the first several hours of ischemic stroke. Stroke should be the first thought when a patient has an acute focal neurologic deficit with headache. Patients with acute focal brain or brainstem dysfunction, headache, and normal CT findings or CT scans that show focal hypodensity need a thorough evaluation for a cause of ischemic stroke or TIA. The evaluation should include assessment of cerebral arteries and the heart for a source of embolism and, in certain circumstances, assessment of the aorta and blood (hypercoagulability or vasculitis profile).
6. **Cervicocephalic arterial dissection** is often—but not always—associated with trauma. When trauma is the cause, symptoms may be delayed for several minutes to hours. Headache, facial pain, or neck pain may be the only symptom. Carotid dissection usually results in ipsilateral, steady, nonthrobbing headache, and ipsilateral Horner syndrome. Pain in the throat and focal cerebral ischemia are also prominent. Vertebrobasilar dissection causes occipital headache or neck pain and may be associated with neck manipulation or whiplash injury. Definitive diagnosis of arterial dissection requires MRI or cerebral angiography. The optimal MRI sequence is fat-saturation cervical MRI—axial view of the artery shows a circle of increased signal intensity (subintimal blood) surrounding a small area of low-signal intensity (normal flow in a narrowed lumen). At cerebral arteriography, the classic finding is a tapered narrowing or occlusion.
7. **Giant cell arteritis** is almost exclusively a disease of persons older than 50 years and is much more prevalent among those older than 60 years. It should be considered when any person older than 50 years has a persistent or new headache. The term *temporal arteritis* is misleading because this condition often affects the short posterior ciliary arteries of the eye and branches of the external carotid artery other than the temporal artery. It can also affect the cerebral and coronary arteries. Possible associated symptoms include visual loss (arteritic AION), temporal tenderness, weight loss, malaise, fever, chills, polymyalgia rheumatica, and jaw claudication. Anemia, leukocytosis, and elevated liver enzyme levels may be present. The CRP elevation is more sensitive and more specific than is ESR elevation. Definitive diagnosis is made by means of temporal artery biopsy. Administration of steroids should be started as soon as serologic results are known. Treatment does not affect biopsy results for at least 2 weeks. Because of the frequent presence of skip lesions, long segments of artery should be obtained, and bilateral biopsy may be necessary.
8. **CVT** is not rare, often goes unrecognized, and occurs as a consequence of a predisposing disease. Diffuse headache due to increased ICP may be the only symptom. Other common symptoms include seizure, focal neurologic deficit, and change in consciousness. Predisposing conditions fall into one of three categories—hypercoagulable state, low-flow state, and vessel wall abnormality. A personal or family history of venous or arterial thrombotic episodes suggests a primary hypercoagulable state. All patients with CVT should undergo a detailed hypercoagulable evaluation. Secondary hypercoagulable states include those associated with late pregnancy, the puerperium, and cancer. Low-flow

states include dehydration, anemia, congestive heart failure, sickle cell disease, and compression of cerebral sinus by tumor. Vessel-wall abnormalities can be caused by trauma, infection, cancer, or inflammation. Because the cerebral sinuses lie in the midline, lesions often are bilateral and parasagittal. Venous edema, infarction, or hemorrhage can occur; edema and infarct cannot be differentiated at cerebral imaging. CT findings often are suggestive but are not enough to make a diagnosis. MRI and MRV are the diagnostic studies of choice. One can also make the diagnosis with conventional cerebral angiography and delayed venous images. CVT should be considered in the evaluation of any patient with a "pseudotumor" syndrome, especially men and thin women (see V.B.9.), any patient with headache and a history consistent with hypercoagulable state, and any patient with headache and bilateral "infarcts" or hemorrhages on cerebral images.

9. **Idiopathic intracranial hypertension (pseudotumor cerebri)** occurs mainly among young obese women. Diagnosis is based on the clinical findings of headache and papilledema, normal findings at cerebral imaging, and elevated opening CSF pressure (more than 250 mm Hg) at LP. Brain tumor and CVT in particular must be ruled out. Papilledema need not be present for diagnosis. The serious sequela of idiopathic intracranial hypertension is blindness due to chronic papilledema. Several drugs can cause intracranial hypertension, mimicking the idiopathic condition; these include tetracycline, aminoglycosides, and vitamin A. The syndrome of intracranial hypertension in a patient taking oral contraceptives should stimulate investigation for CVT because oral contraceptives can exacerbate or cause a hypercoagulable state.
10. **Unruptured AVM** can cause migraine headaches. If an apparent migraineur always has hemicranial headaches on the same side and there is no known family history of migraine, one should use MRI to rule out unruptured AVM. It is likely that ischemia or rapid changes in cerebral blood flow incite spreading cortical excitation/depression and a migraine attack.
11. **Postcarotid endarterectomy** headaches occur in approximately 40% of patients undergoing the procedure. Similarly, headaches may occur in patients who have had **postcarotid angioplasty and stenting.** The headache usually develops several hours to days after the procedure, is ipsilateral to the side of the revascularization, and resembles a migraine. Patients with a history of migraine may have a typical attack, and nausea may be present. Although the headache usually lasts only a few hours and the neurologic symptoms usually resolve without sequelae, a migrainous headache may herald the onset of reperfusion syndrome with ipsilateral vasogenic cerebral edema, seizures, and intracerebral hemorrhage. Patients with bilateral high-grade carotid stenoses and chronic cerebral hypoperfusion pre-procedure are at particular risk for reperfusion syndrome. As is the case with AVM, the rapid change in cerebral blood flow may incite spreading cortical excitation/depression and migrainous phenomena.
12. **Bell's palsy,** idiopathic or herpetic mononeuropathy of cranial nerve VII, often is associated with retroauricular pain. Pain may be the first symptom and may be severe enough to be the patient's chief symptom, rather than the ipsilateral facial weakness involving the forehead, eye closure, and lips.
13. **Cerebral tumors and abscesses** usually manifest similarly as gradually progressive headache over weeks to months. They may also be associated with gradually progressive neurologic deficit. Both primary brain tumors and metastatic lesions can occur acutely if associated with hemorrhage or seizure. Abscesses frequently cause seizures and can be associated with fever and other signs of sepsis. Any patient with a known history of cancer and new headache should be evaluated for cerebral metastasis. Colloid cysts of the third ventricle may manifest as positional headaches, as in II.C.2.
14. **Dental abscesses** usually manifest as oral or jaw pain, but if the patient is not treated, these abscesses may cause more diffuse headache.
15. **Sinusitis** is a much less common cause of acute headache than is generally imagined. A sensation of nasal congestion is common in migraine owing to vasodilatation in the external carotid territory; this can even cause clear nasal drainage or nose bleed. Surgery for sinusitis should not be undertaken to manage the headache alone because the headache associated with sinus congestion is usually due to migraine. The diagnosis of sinusitis is more likely if the headache is associated with fever, purulent nasal discharge, and increased densities in the sinuses on CT scans.

16. **Trigeminal neuralgia** usually is described as a sharp or burning pain rather than an ache and most commonly occurs unilaterally in the maxillary distribution of the trigeminal nerve. It can occur sporadically or represent a symptom of multiple sclerosis (see Chapter 40).
17. **Low-CSF-pressure headache** can occur when CSF pressure is abnormally low, as occurs after LP (post-LP headache) or after nerve root sleeve trauma and subsequent CSF leak. Symptoms typically resolve in the supine position and recur when the patient is upright.
18. **Acute glaucoma** often manifests as periorbital headache. Pupillary changes, conjunctival injection, lens clouding, and a globe hard to palpation are typical. Elevated intraocular pressure confirms the diagnosis.
19. **Arterial hypertension,** per se, does not cause headache. Rather, it often occurs as a result of a syndrome also associated with headache such as migraine, stroke, hypertensive encephalopathy, eclampsia, pheochromocytoma, or ingestion of cocaine, amphetamines, phenylpropanolamine, or monoamine oxidase inhibitors.

VI. DIAGNOSTIC APPROACH

The diagnosis of primary headache conditions is based on a supportive detailed history and normal findings at neurologic examination. If the clinician has any suspicion at all that the patient may be having a secondary headache, a series of diagnostic tests is indicated to determine the cause of headache. Many of the conditions that cause secondary headache are fatal or disabling if the patient is left untreated. Fortunately, in many cases, the conditions can be managed. Figure 20.2 depicts a diagnostic algorithm for patients with suspected acute secondary headache. If a patient has any one of the clinical features suggestive of secondary headache, the diagnostic evaluation should be undertaken, beginning with laboratories and noncontrast CT.

VII. REFERRAL

A. **Primary headache.** Migraine, cluster, "tension-type," and medication-overuse (analgesic rebound) headaches are chronic conditions that manifest acutely. The proper management of primary headache conditions requires long-term care. Once the acute-care clinician diagnoses primary headache and offers emergency treatment, he or she is obligated to counsel the patient regarding the importance of long-term care and to refer the patient to a neurologist or generalist for definitive treatment. Increased patient education leads to improved patient care and lower health care costs by not spending emergency department resources on patients with recurrent headache.

B. **Secondary headache.** After initial diagnosis and emergency management, the definitive treatment of patients with secondary headache usually requires admission to the hospital and referral to a specialist. Neurointerventionalists and neurosurgeons care for patients with SAH, neurosurgeons for patients with subdural or epidural hematoma. Patients with intracranial masses need immediate referral to a neurologist and often a neurosurgeon as well. If the mass is a tumor, referral to a neuro-oncologist may be necessary and, if the mass is an abscess, referral to a specialist in infectious diseases is appropriate. Most patients with sinusitis and headache are best cared for by a generalist or infectious disease expert. Referral to an otolaryngologist is appropriate if surgery is deemed necessary. Acute-care clinicians should initiate treatment for patients who have suspected giant cell arteritis with high-dose steroids, then refer immediately to a neurologist or rheumatologist for long-term steroid therapy and an ophthalmologist or neurosurgeon for temporal artery biopsy. Patients with CVT need immediate referral to a neurologist or primary-care physician for anticoagulation and hypercoagulability evaluation and to an ophthalmologist to follow visual fields carefully and perform optic nerve sheath fenestration if necessary.

Recommended Readings

Bounes V, Edlow JA. Migraine: diagnosis and pharmacologic treatment in emergency department. *Eur Rev Med Pharmacol Sci*. 2011;15:215–221.

Cady RK, Schreiber CP. Sinus problems as a cause of headache refractoriness and migraine chronification. *Curr Pain Headache Rep*. 2009;13:319–325.

De Luca GC, Bartleson JD. When and how to investigate the patient with headache. *Semin Neurol*. 2010;30:131–144.

Fischer C, Goldstein J, Edlow J. Cerebral venous sinus thrombosis in the emergency department: retrospective analysis of 17 cases and review of the literature. *J Emerg Med*. 2010;38:140–147.

Ju YE, Schwedt TJ. Abrupt-onset severe headaches. *Semin Neurol*. 2010;30:192–200.

Lauritzen M, Dreier JP, Fabricius M, et al. Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cereb Blood Flow Metab*. 2011;31:17–35.

Ramchandren S, Cross BJ, Liebeskind DS. Emergent headaches during pregnancy: correlation between neurologic examination and neuroimaging. *AJNR Am J Neuroradiol*. 2007;28:1085–1087.

Schankin CJ, Ferrari U, Reinisch VM, et al. Characteristics of brain tumor-associated headache. *Cephalalgia*. 2007;27:904–911.

Wagner WH, Cossman DV, Farber A, et al. Hyperperfusion syndrome after carotid endarterectomy. *Ann Vasc Surg*. 2005;19:479–486.

Yuh EL, Dillon WP. Intracranial hypotension and intracranial hypertension. *Neuroimaging Clin N Am*. 2010;20:597–617.

CHAPTER

21 Approach to the Patient with Chronic and Recurrent Headache

David S. Lefkowitz

Most chronic, recurrent headaches represent a benign headache syndrome; however, headache may also be a symptom of serious CNS or systemic disease. Therefore, the differentiation of primary from secondary headache is an important goal of evaluation.

Primary Headache Disorders

Migraine, tension-type headache, cluster headache, and chronic daily headache represent the overwhelming majority of headaches seen in primary care. Chronic daily headache is more common in referral-based practices specializing in headache. The International Headache Society (IHS) revised its classification system in 2004 and defines headache syndromes on the basis of signs and symptoms. The characteristics of the primary recurrent headaches are described below and in Table 21.1.

I. MIGRAINE

Migraine is now thought to be due to the disturbed function of the trigeminovascular system rather than a primary abnormality of blood vessels. Therefore, the IHS classification no longer refers to migraine as "migraine headache of the vascular type."

A. The clinical characteristics of migraine are outlined as follows in the IHS criteria.

1. Duration of untreated or unsuccessfully treated headache is 4 to 72 hours.

2. The quality of the pain fulfills at least two of the following: unilaterality, pulsatility, moderate to severe intensity, and aggravation by routine physical activity.

3. At least one of the following is present: nausea or vomiting, photophobia and phonophobia.

4. The diagnosis of migraine and other benign headache syndromes requires the exclusion of organic disease.

5. There should be at least five such episodes if there is no aura or at least two if an aura is present.

B. Migraine with aura (formerly classical migraine) is associated with focal neurologic symptoms and signs. It is a manifestation of cortical spreading depression. Typical migraine auras include homonymous visual disturbance, unilateral paresthesia or numbness, unilateral weakness, aphasia, or unclassifiable speech disturbance. Sensory auras typically have a cheiro-oral distribution and "march" from one body part to another. By definition, the aura meets at least three of the following criteria:

1. It consists of one or more fully reversible positive or negative symptoms of focal cerebral or brainstem dysfunction.

2. One aura symptom develops gradually over 5 or more minutes. If two or more symptoms occur, they do so in succession.

3. No aura symptom lasts more than 60 minutes, or proportionately longer if there is more than one.

4. Headache follows within 1 hour of the aura, precedes the aura, or occurs simultaneously with it. An aura need not begin before the headache.

C. Migraine auras may be prolonged or permanent. Migraine with persistent aura occurs in patients when one aura symptom persists for more than 7 days and neuroimaging studies remain normal. Migrainous infarction is defined as a complication of migraine in

TABLE 21.1 Characteristics of Benign Recurrent Headache Disorders

Characteristic	Migraine	Tension Type	Cluster	Chronic Daily
Age at onset	10–30 y	Any age	Middle age	3rd–4th decade
Gender	F > M	F > M	M > F	F > M
Duration	4–72 h	30 mo–7 d	15–180 mo	Constant or nearly constant
Frequency	Variable	Occasional	Daily for weeks to months	Daily or constant
Time of day	Any time	Later in day	Nocturnal	Constant
Quality	Pulsatile	Dull, aching, band like	Severe, boring	Variable
Location	Retroorbital, temporal, hemicranial or holocephalic	Bilateral, temporal or occipitonuchal	Unilateral, retroorbital	Variable
Associated symptoms	Nausea, vomiting, photophobia, phonophobia with or without neurologic accompaniments	Other symptoms rare, associated with stress in episodic form	Ipsilateral autonomic signs and symptoms	Migraine history, analgesic overuse and psychopathology are common

which aura does not completely resolve within 7 days and there is evidence of infarction on imaging.

D. Migraine aura without headache (migraine equivalent) occurs when the aura occurs without headache.

E. Migraine may be triggered by specific endogenous or environmental factors, including ingestion of tyramine-containing foods or alcohol, changes in sleep pattern, and emotional stress. There is also a relation with hormonal factors. Migraine is more frequent in women after menarche. For most women, it is more frequent or severe at or around menses, and the headaches often improve after menopause.

F. The new classification system recognizes a subgroup with chronic migraine that has more than 15 headache days per month or 180 per year.

II. TENSION-TYPE HEADACHE

Tension-type headache replaces the terms "tension" or "muscle contraction" headache because of evidence that muscle tension is not the underlying mechanism of pain.

A. Clinical characteristics of tension-type headache include the following:

1. Headache duration is 30 minutes to 7 days.

2. The pain meets two of the following criteria: pressing or tightening quality, nonpulsatility, mild to moderate intensity, bilaterality, and lack of aggravation by routine physical activity.

3. Absence of nausea or vomiting, although anorexia does occur. Photophobia or phonophobia may occur but not simultaneously.

4. No evidence of organic disease.

5. There may or may not be tenderness of pericranial muscles to palpation.

6. A history of 10 similar headaches.

B. Tension-type headache is episodic when there are fewer than 15 headache days per month or 180 days per year for at least 6 months and chronic when headache frequency exceeds these limits.

III. BENIGN RECURRENT HEADACHE

Migraine without aura and episodic tension-type headache may be difficult to differentiate in some patients because both can be bilateral, nonthrobbing, moderately severe, and associated with anorexia, photophobia, or phonophobia without violating IHS criteria. Some patients may have mixed headaches with features of both or have both types independently. It has been postulated that migraine and tension-type headache are phenotypic expressions of a common abnormality of serotoninergic nociceptive mechanisms referred to as benign recurrent headache. As headache frequency increases, the severity and association with autonomic and neurologic symptoms decrease.

IV. TRIGEMINAL AUTONOMIC CEPHALGIAS

This is a family of disorders manifested by brief, intense, unilateral headaches associated with signs of parasympathetic hyperactivity. The most frequent is cluster headache. Trigeminal autonomic cephalgias are associated with activation of the inferior posterior hypothalamus.

A. Cluster headache. The clinical manifestations of cluster headache are quite characteristic, and the disorder is readily diagnosed from the history and physical examination.

1. A diagnosis can be made using IHS criteria after five or more attacks with the following features:

a. Severe unilateral orbital, supraorbital, or temporal pain lasting 15 to 180 minutes. The pain is usually described as boring.

b. Patients invariably have at least one ipsilateral autonomic sign, including conjunctival injection, eyelid edema, lacrimation, nasal congestion or rhinorrhea, forehead and facial sweating, miosis, or ptosis and agitation.

c. Attacks occur from once every other day to eight times a day. There is a tendency for attacks to occur at the same time each day or to awaken the patient from sleep, usually in the early morning during rapid eye movement sleep.

2. The typical episodic pattern consists of periods of headache lasting 1 week to 1 year separated by remissions of at least 2 weeks. Chronic cluster occurs when headaches persist for at least 1 year without interruption or if remission lasts <2 weeks. Secondary chronic cluster headache occurs if chronic cluster develops after a period of typical episodic headaches.

3. During cluster periods, headache may be precipitated by alcohol, nitrates, and histamine.

B. Cluster headache variants. Several headache disorders, some of which are of mostly historical significance, are thought to represent cluster headache. Raeder originally described a parasellar syndrome of trigeminal pain, oculosympathetic paresis, and cranial nerve dysfunction. The term Raeder's syndrome came to be used for non-neuralgic head pain and oculosympathetic paresis without other cranial nerve palsies. "Lower-half headaches" such as Sluder's syndrome, sphenopalatine neuralgia, vidian neuralgia, and greater superficial petrosal neuralgia, which manifest as facial pain and ipsilateral nasal congestion or rhinorrhea may also represent cluster headache.

C. Chronic paroxysmal hemicrania is an unusual disorder mainly affecting women with multiple, brief, unilateral, cluster-like headaches occurring at least five times a day and absolute responsiveness to indomethacin. The pain is generally severe and lasts <30 minutes. There is at least one ipsilateral autonomic symptom during the headache including conjunctival injection, lacrimation, rhinorrhea, nasal congestion, eyelid edema, or oculosympathetic paresis.

D. Short-lasting unilateral neuralgiform cephalgia with conjunctival injection and tearing (SUNCT) is the rarest of the trigeminal autonomic cephalgias. The headaches are more frequent than in the other syndromes, are briefer and less severe, and autonomic involvement generally consists of ipsilateral lacrimation and conjunctival injection. The pain is sharp or pulsating and lasts <4 minutes. There may be as many as 200 attacks a day. Patients without conjunctival injection or lacrimation but with other autonomic symptoms may have a subgroup of this disorder.

V. OTHER PRIMARY HEADACHE DISORDERS

A. Hemicrania continua is a type of chronic daily headache that is strictly unilateral, constant, moderately severe, and usually associated with autonomic signs such as lacrimation, conjunctival injection, rhinorrhea or nasal congestion, ptosis or miosis, and completely responsive to indomethacin.

B. Idiopathic stabbing headache has previously been referred to as jabs and jolts or ice pick pains. It is frequently associated with other primary headaches such as migraine or cluster headache. The clinical pattern is distinctive and diagnosed as follows:

1. Pain is localized to the head, mainly to the distribution of the ophthalmic division of the trigeminal nerve.
2. The pain is stabbing in quality, lasts for a fraction of a second, and may occur singly or in series.
3. Headache recurs at irregular intervals of hours to days.
4. There are no structural changes at the site of the pain or in the distribution of the affected nerve.

C. Primary cough headache. This is a bilateral headache precipitated by Valsalva. Some patients with cough headache have posterior fossa mass lesions or cranio-vertebral junction abnormalities.

VI. CHRONIC DAILY HEADACHE

A. Chronic daily headache is a primary headache disorder in which headaches occur at least 15 days per month. The new IHS classification system recognizes chronic forms of migraine and tension-type headache.

B. Most patients with chronic daily headache evolve from a pattern of episodic migraine.

C. New daily persistent headache is a form of chronic daily headache, which arises acutely without antecedent migraine or tension-type headache and remains constant and unremitting from onset. Most patients can specifically identify the time of onset. The pain is bilateral, nonpulsatile, moderately severe, and unaffected by routine exertion. There may be mild nausea, photophobia, or phonophobia.

D. Analgesic rebound headache. Rebound or withdrawal headache related to overuse of narcotics, butalbital-containing analgesics, ergotamine, or over-the-counter pain medications is frequently a factor in chronic daily headache. These patients have a rhythmic cycle of headache and medication use. The patient awakens with early morning headache resulting from medication withdrawal, and the headache is relieved only by the next dose of medication. Patients may begin to use analgesics in anticipation of pain. Other symptoms of medication withdrawal include irritability, asthenia, and insomnia.

Secondary Headache Disorders

Headache may be a symptom of a variety of disorders of the nervous system.

I. TUMOR

A. Head pain among patients with brain tumors arises from traction or pressure on pain-sensitive intracranial structures or from production of increased intracranial pressure (ICP).

B. There is nothing pathognomonic about headache associated with brain tumor. In most cases, headache is dull, aching, or pressure-like in quality. The headache is intermittent and moderately severe in most patients. Bending or Valsalva may aggravate the pain. Headache from brain tumor rarely mimics migraine.

C. The "typical" history of severe headache worse in the morning and associated with nausea or vomiting or a history of postural, cough, or exertional headache is relatively infrequent.
D. Unilateral headache usually is on the side of the lesion. Bilateral headache usually is due to increased ICP or either midline or bilateral tumor.
E. Supratentorial tumors generally produce frontal or bifrontal headache. Infratentorial tumors generally cause occipital pain.
F. Increased ICP produces severe headache in the frontal area, vertex, or neck with nausea and vomiting.
G. Involvement of the dura or skull may produce localized pain.

II. CEREBROVASCULAR DISEASE

A. Intracranial hemorrhage. Headache, nausea, and vomiting are more commonly associated with intracranial hemorrhage than with ischemic stroke. In some patients, recurrent subarachnoid hemorrhage (SAH) may resemble migraine. Patients with aneurysmal SAH often have a warning leak or sentinel headache several days to months before substantial hemorrhage occurs.
B. Unruptured aneurysms. It is controversial how often unruptured aneurysms cause recurrent headache. In some patients, sudden onset of an intense headache with normal imaging and spinal fluid, referred to as thunderclap headache, simulates SAH. Unruptured aneurysms and segmental vascular narrowing have been reported in patients with thunderclap headache. Data suggest that in most of these cases the aneurysm is incidental. Prospective data demonstrate that SAH is rare in patients with recurrent primary thunderclap headache.
C. Arteriovenous malformation (AVM). Chronic headache occurs in approximately 15% of patients with AVMs. These headaches may be clinically indistinguishable from migraine. This relation may be coincidental because migraine is common in the general population and AVMs are rare in large series of patients with migraine who undergo imaging studies.
D. Ischemic stroke. Headache occurs in 30% to 40% of patients with cerebral infarction and 25% to 40% of those with transient ischemia. It is usually nonthrobbing, ipsilateral to the infarct, and self-limited. In patients with chronic or recurrent headache associated with stroke, the following differential diagnoses should be considered.

1. **Cervicocephalic dissection.** An ipsilateral throbbing or steady headache, with or without neck or jaw pain, frequently accompanies carotid artery dissections. Dissection may produce fixed or reversible neurologic deficits. Oculosympathetic paresis, visual scintillations, and dysgeusia are also clues to this diagnosis. Dissections may be overlooked when they occur without a previous history of trauma or after relatively trivial injuries.
2. **Migrainous stroke and late-life migraine accompaniments.** When headache recurs in association with focal neurologic deficit, it may be challenging to distinguish between migrainous accompaniments from atherosclerotic cerebrovascular disease, especially in elderly patients with stroke risk factors. There need not be a preexisting history of migraine or a severe headache during the episode. Fisher suggested the following criteria for late-life migraine accompaniments.
   a. Scintillations or other typical visual displays that may expand or "build up" after onset.
   b. A sensory "march" from one body part to another or spread to the opposite side of the body.
   c. Progression from one accompaniment to another without delay.
   d. Episodes may be stereotyped, which should be less common with embolism.
   e. Headache is frequently associated with the episode.
   f. The attacks occur in characteristic flurries during mid- or late-life and have a benign course.
   g. Exclusion of other causes of focal deficit, including atherosclerosis.

E. Sinovenous thrombosis. Occlusion of a major dural sinus frequently produces headache and papilledema indistinguishable from pseudotumor cerebri. Sinovenous occlusion should be suspected whenever acute or subacute neurologic dysfunction manifests as altered consciousness, focal deficits, seizures, or evidence of an increased ICP.

III. HEADACHES RESULTING FROM DISORDERS OF ICP

A. Idiopathic intracranial hypertension (benign intracranial hypertension and pseudotumor cerebri).
1. The primary features of this disorder are headache and visual disturbance (enlargement of the blind spot, transient visual obscurations, and progressive visual loss) resulting from elevated ICP. There may also be pulsatile tinnitus, dizziness, and nausea.
2. Idiopathic intracranial hypertension occurs most often in women and is frequently associated with obesity and menstrual irregularities.
3. Physical findings are limited to papilledema and abducens nerve palsies. Papilledema may be unilateral, asymmetric, or absent.
4. CSF is acellular with elevated pressure. The protein may be low.
5. Imaging may show slit-like ventricle, acquired tonsillar ectopia, or an empty sella, but no mass lesion.
6. Most cases are idiopathic but potential etiologies include vitamin A intoxication, steroid withdrawal, hypoparathyroidism, systemic lupus erythematosus (SLE), or medications (tetracycline and nalidixic acid). In some patients, imaging reveals superior sagittal or lateral sinus thrombosis. Sinovenous occlusion associated with ear infection has been referred to by the misnomer "otitic hydrocephalus."
7. Idiopathic intracranial hypertension without papilledema should be considered in the differential of chronic daily headache.

B. Hydrocephalus.
1. Headache is not usually a feature of communicating hydrocephalus.
2. Headache is common with obstructive hydrocephalus. It is usually occipital and may be associated with neck pain or stiffness, vomiting, or visual abnormalities. The headache may be present on awakening and more severe in the morning. Obstructive hydrocephalus resulting from intraventricular tumors may cause positional headache and life-threatening increases in ICP.

C. Intracranial hypotension. The typical history includes postural headache with or without nausea and dizziness, which is worsened or initiated by standing and relieved by recumbency. The diagnosis is obvious when there is a history of a preceding lumbar puncture (LP).
1. **Post-LP** headache may occasionally be protracted or complicate evaluation of patients with chronic or recurrent headaches from other causes. Demographic features associated with post-LP headache are youth, female gender, and low body mass index. Technical aspects affecting the risk of post-LP headache include needle diameter, use of cutting (Quincke) needles, and orientation of the bevel but not duration of recumbency after the procedure or hydration.
2. CSF hypotension may also occur as a result of CSF leaks from head trauma, Valsalva's maneuver, or nerve-root avulsion.
3. The diagnosis may be confirmed by low-CSF pressure on repeat LP. MRI demonstrates diffuse dural enhancement, descent of the cerebellar tonsils, and subdural fluid collections.

IV. PHEOCHROMOCYTOMA

Approximately 10% of patients with pheochromocytoma present with headache and paroxysmal hypertension. The headache is usually bifrontal, severe, and throbbing. It may be exacerbated by coughing, bending, straining, or lying flat.

V. HEADACHE OF RHINOSINUSITIS

A. Current criteria require that headache of rhinosinusitis be associated with acute or acute on chronic sinus infection demonstrated by objective means such as nasal endoscopy or

facial CT, a temporal relationship with onset of sinusitis and resolution after successful treatment of the sinus infection.

B. Chronic changes such as mucoperiosteal thickening are not associated with headache.

C. Most patients with self-reported sinus headaches meet IHS criteria for migraine or respond to triptans.

VI. INFLAMMATORY DISORDERS

A. Giant cell arteritis.

1. This disorder is rare before age 50 but increases in incidence with advancing age.

2. Headache is almost invariably present. Pain is often localized to the temple and is sharp, throbbing, or boring in quality. There may be constitutional symptoms, joint complaints (polymyalgia rheumatica), or jaw claudication. Blindness from ischemic optic neuropathy is the most feared complication. Diplopia may arise from ischemia of oculomotor nerves or extraocular muscles.

3. Physical findings include a tender, nodular, nonpulsatile, thickened superficial temporal artery.

4. Diagnosis. The Westergren erythrocyte sedimentation rate (ESR) is elevated in approximately 85% of patients. Other common laboratory abnormalities include elevated C-reactive protein, thrombocytosis, and anemia. Definitive diagnosis requires superficial temporal artery biopsy, but the biopsy may be negative because of patchy involvement (skip lesions).

B. SLE.

1. Migrainous headaches, often with focal auras, occur frequently in patients with systemic lupus. Visual scintillations have been reported anecdotally as the presenting symptom of lupus. In a case-controlled prospective study of patients with SLE, there was a higher incidence of migraine, a higher percentage of migraine with aura, and later age of migraine onset than in controls. There was also a tendency for headaches to parallel the activity of the lupus and sometimes to respond to steroids or immunosuppressants.

2. There is no proven association of antiphospholipid antibodies to migraine in SLE patients.

VII. POST-TRAUMATIC HEADACHES

A. Postconcussion syndrome is a distinct clinical entity following relatively minor head injuries that is manifested by recurrent headache, memory disturbances, irritability, difficulty concentrating, dizziness, and depressive symptoms. Symptoms usually resolve within 6 months.

B. Chronic subdural hematoma may present with headache, seizures, or focal neurologic deficits.

C. Occipital neuralgia. The occipital nerve may be traumatized directly or compressed by spasm of the trapezius or semispinalis capitis muscle. There is usually a lancinating, neuralgic component to the pain, a Tinel's sign over the occipital condyle and decreased sensation over the ipsilateral occipital scalp.

D. Post-traumatic migraine and tension-type headaches. In some patients, head trauma may precipitate headaches identical in quality to migraine or tension-type headache or aggravate preexisting ones. Post-traumatic cluster headache has also been reported. In some patients, headache is associated with scarring at the site of a scalp laceration and is relieved by infiltration of a local anesthetic.

E. Post-traumatic dysautonomic cephalalgia. Throbbing headaches associated with nausea, photophobia, and signs of ipsilateral sympathetic overactivity, such as sweating and mydriasis, occur as delayed sequelae of penetrating neck injuries that damage the sympathetic fibers in the carotid sheath. This disorder should not be confused with cluster headache, which it superficially resembles.

VIII. TEMPOROMANDIBULAR JOINT DYSFUNCTION

Temporomandibular joint (TMJ) dysfunction is believed to be a myofascial syndrome related to dental malocclusion or bruxism. It may cause recurrent preauricular or temporal pain radiating into the neck. The pain is typically aggravated by chewing and is frequently worse in the morning. Physical findings include lateral jaw deviation and crepitus of the joint on opening the mouth and tenderness or spasm of the masticatory muscles.

IX. TRIGEMINAL NEURALGIA

Trigeminal neuralgia is often mentioned in the differential diagnosis of cluster headache, although typical trigeminal neuralgia is rarely confused with other entities. Onset usually occurs late in life except when it is a manifestation of multiple sclerosis.

A. The IHS defines trigeminal neuralgia as follows:

1. Paroxysmal attacks of facial or frontal pain lasting a few seconds to <1 minute.

2. The attacks have at least four of the following characteristics:
   a. Distribution along one or more divisions of the trigeminal nerve.
   b. Sudden, intense, sharp, superficial, stabbing or burning quality.
   c. Severe intensity.
   d. Precipitation by stimulation of trigger areas or by daily activities such as eating, talking, washing the face, or cleaning the teeth.
   e. The patient is asymptomatic between the paroxysms.
   f. Absence of neurologic deficit.
   g. Attacks are stereotyped.

3. Most cases result from microvascular compression of the trigeminal nerve, but secondary causes include cerebellopontine angle tumors and vascular malformations.

Clinical Assessment

I. HISTORY

The history is the most important factor in the accurate diagnosis of headache. It is usually helpful to ask the patient to describe a typical headache from its onset. As many as 30% to 40% of headache patients have more than one headache type, and an accurate description of each type should be obtained. Disorders of structures in or near the head may be perceived as headache. Therefore, the physician must inquire about general symptoms and signs of nervous system dysfunction in addition to a detailed medical history. The headache history should specifically include questions regarding the following areas.

A. Age of onset. Most benign headache syndromes start early in life, usually between childhood and the third decade, although tension-type headache may begin at any time. Late onset may suggest a more serious condition.

B. Localization of pain. The location of headache may help in determining its etiology. Migraine is frequently unilateral, alternates sides, and involves the temple or retro-orbital area. Tension-type headache is usually bilateral, frontal, or occipital, and radiates into the neck and shoulders. Brief attacks of strictly unilateral orbital pain suggest cluster headache or chronic paroxysmal hemicrania. Dental, ocular, and sinus disorders often produce frontal pain. The site of headache may be of localizing value in patients with mass lesions.

C. Temporal pattern. Headache syndromes may have characteristic patterns of duration and frequency. In general, longer-lasting headaches tend to be benign, particularly when headache is constant over more than several months without change in character or new signs. Headache resulting from meningitis may be constant, but not usually over

a prolonged duration. Benign headache syndromes typically produce episodic headache. For instance, migraine usually lasts several hours and occurs several times a month. Cluster headache has a characteristic periodicity. Acute tension-type headache is usually brief and associated with emotional stress, but in its chronic form, tension-type headache becomes more frequent, prolonged, or constant and loses its association with psychosocial stressors. The mode of onset may also be helpful. Does the headache begin gradually or start suddenly? Sudden onset of headache is of greater concern because it may indicate intraparenchymal or SAH.

D. Quality and severity of pain. These may be difficult for patients to verbalize and the interviewer may need to offer guidance to elicit the history. Migraine and headache associated with fever are usually throbbing and pulsatile, for instance. Tension-type headache is usually described as dull and nagging, tight and constricting, or bandlike. Tumor and meningitis typically produce a steady, aching pain. Severity of pain can be ranked on a scale of 1 to 10. An indirect indicator of severity is interference with work and social activities.

E. Prodromal and associated symptoms. Symptoms that precede or coincide with headache may be clues to the nature of the underlying headache. The patient with migraine may have premonitory mood or behavioral changes for several days prior to onset. Visual scintillations and fortification spectra are typical migraine prodromes, but visual symptoms may also be associated with carotid dissections and occipital AVMs. Ipsilateral autonomic features are almost always present in cluster headache, the paroxysmal hemicranias, hemicrania continua, and SUNCT.

F. Precipitating factors. Provoking factors may suggest the diagnosis. Examples include precipitation of an attack of trigeminal neuralgia by cutaneous stimulation or of migraine by ingestion of certain foods or alcohol, stressful life events, glare, hypoglycemia, or sleep deprivation. Chewing may trigger pain in patients with TMJ dysfunction or giant cell arteritis. Avoidance of triggers may also be helpful in treatment.

G. Sleep onset. Migraine, hypnic, and cluster headaches may awaken patients from sleep. Tension-type headache rarely does. Headaches are generally worse in the mornings in patients with sleep apnea and increased ICP.

H. Relieving or exacerbating factors. Patients with migraine typically report exacerbation with movement, bending, straining, and coughing and relief with lying flat, avoiding bright light and sometimes by pressure over the superficial temporal artery or after vomiting. Post-LP headache is characteristically modified by posture.

I. Family history. About 20% to 60% of patients with migraine report at least one affected family member. However, this is not unexpected because 6% of men and 18% of women in the general population have migraine.

II. PHYSICAL EXAMINATION

In addition to a thorough general and neurologic examination, certain areas require special attention.

A. Vital signs should be checked for fever and hypertension.

B. Inspection, palpation, and percussion of the skull should be performed to check for tenderness or scarring, which may be signs of trauma. There may be tenderness at the site of a skull neoplasm. Percussion over the site of a tumor or subdural hematoma may also produce pain. In children, head circumference should always be measured.

C. Assessment of the ears, tympanic membranes, and mastoids may reveal evidence of otitis or mastoiditis.

D. Evaluation of the TMJs. There may be local tenderness, crepitus or lateral jaw deviation with mouth opening or closing. This can be felt externally or with the examiner's fingers in the external auditory canals. When TMJ dysfunction results from muscle spasm, the joint is tender to direct palpation but not to palpation through the ear canal.

E. Palpation of glandular and lymphatic tissues. Examination of the soft tissues of the neck may reveal evidence of infection or malignancy, sarcoidosis, or Behçet's syndrome.

F. Inspection of the teeth and oropharynx. In some patients, headache may be referred from dental disease, although headache rarely occurs without concomitant tooth pain. Percussion of the teeth and inspection for caries and periodontal disease may reveal a dental origin of pain. Percussion of the maxillary teeth may also hint at maxillary sinusitis, which can arise from dental root infection.

G. Assessment of the nose and paranasal sinuses. The nasal mucosa should be examined for polyps, septal deviation, and secretions. The maxillary and frontal sinuses may be palpated or percussed. The sinuses can also be transilluminated with a flashlight in a darkened room. The ethmoid and sphenoid sinuses cannot be adequately evaluated at the bedside.

H. Assessment of the eyes. Ocular causes of headache are uncommon but patients frequently consult an ophthalmologist or optometrist before seeking a neurologic opinion. Eye strain and refractive errors rarely prove to be the cause of chronic headache. Nevertheless, examination of the eyes may reveal papilledema or abducens palsy resulting from increased ICP, optic disc pallor from a compressive lesion, or ischemic optic neuropathy associated with giant cell arteritis. Acute glaucoma may sometimes present primarily with head pain.

I. Assessment of the extracranial vasculature is especially important in cases of suspected giant cell or temporal arteritis, in which the superficial temporal artery may be tender, nodular, and nonpulsatile. Bruits may result from arterial stenosis or increased venous outflow in patients with AVMs. Increased collateral flow may be a source of headache when there is extracranial vascular disease. In patients with migraine, compression of the superficial temporal artery may temporarily relieve the pain.

J. Palpation of the scalp and neck musculature and neck mobility. Tenderness of the pericranial muscles and limited or painful range of motion of the neck may suggest tension-type headache or spinal pathology. Spinal disease may cause headache referred to the frontal area. Resistance to passive anteroposterior neck movement, Kernig's and Brudzinski's signs are indications of meningeal irritation due to CNS infection or subarachnoid bleeding.

K. A low hairline may be a clue to craniovertebral junction abnormalities such as a Chiari's malformation, basilar impression, or basilar invagination.

Clues to Structural Disease

I. INDICATORS OF STRUCTURAL DISEASE

Recurrent attacks of an acute recurrent headache are usually migraine. Chronic nonprogressive headache usually represents analgesic overuse, benign intracranial hypertension, or chronic tension-type headache. Features that suggest structural disorders are discussed in this section:

A. Altered consciousness or behavior. Although loss of consciousness during headache may result from vasovagal syncope or basilar migraine, in most cases it is a sign of increased ICP, seizure activity, or ischemia. Sudden headache with altered consciousness may represent SAH. Changes in cognitive function may also accompany structural lesions.

B. Neurologic deficit developing simultaneously with or following the onset of headache. Migraine auras usually precede the headache, although this is not required by definition. For the other benign headache disorders except cluster headache, nonspecific subjective neurologic symptoms occur more often than objective signs of neurologic dysfunction. When a neurologic deficit develops at or after onset of headache, differential considerations include tumor, stroke, and abscess.

C. Headache associated with fever or meningeal signs should always suggest infection. Recurrent meningitis may occur in patients with anatomic defects, after splenectomy, or immune compromise. Noninfectious causes of recurrent meningitis include craniopharyngiomas, dermoid cysts, sarcoidosis, Behçet's syndrome, and Vogt–Koyanagi–Harada's syndrome. Recurrent aseptic meningitis associated with large mononuclear endothelial cells is referred to as Mollaret's meningitis. It has been associated with Herpes simplex infection. Tuberculous and fungal meningitides are likely to present chronically.

SAH may also produce meningismus and low-grade fever. Fever and headache may accompany sinusitis or dental abscess, but the physician should keep in mind the possibility of intracranial complications of extracranial infections of the head and neck, including sinovenous thrombosis and brain abscess.

D. Headache occurring exclusively on one side over time is referred to as side-locking. It has traditionally been described as a sign of structural disease, particularly vascular abnormalities. In reality, benign headache syndromes such as migraine, cluster headache, and atypical facial pain may consistently affect one side of the head.

E. Onset after age 50. Benign headache syndromes generally begin early in life. Exceptions are cluster headache, which usually begins in middle age, and hypnic" headache.

F. Change in character of preexisting headache or response to treatment. A patient with chronic recurrent headache can develop a second disorder. Therefore, the clinician should carefully approach the patient with a change in the pattern or quality of chronic headaches.

G. Vomiting preceding headache by days to weeks, with or without preceding nausea, may be a sign of increased ICP.

H. Headache associated with paroxysmal hypertension. Pheochromocytomas cause headache, tachycardia, tremor, nausea, or diaphoresis. When the tumor is located in the bladder, symptoms may follow urination.

I. Associated endocrine changes. The association of subacute or chronic headache with signs of secondary hypothyroidism, galactorrhea, hypo- or hypercortisolism, or other evidence of pituitary dysfunction raises suspicions of a sellar lesion such as a pituitary adenoma. Hypopituitarism may also occur with craniopharyngiomas.

J. Headache precipitated by rapid changes in head position or head movement. Rapid changes in head position may produce pain when there is an intracranial mass. Intraventricular lesions such as colloid cysts of the third ventricle may cause obstructive hydrocephalus with a change in posture.

K. Headache initiated by Valsalva's maneuver or associated with exercise or sexual activity. Although migraine is often exacerbated by Valsalva's maneuver, the onset of headache with Valsalva's maneuver is more ominous. About 10% of patients with exertional or cough headache have an underlying structural abnormality such as a craniocervical junction abnormality, posterior fossa mass, or pituitary tumor. These patients should always have MRI scans. Some patients with exertional headache have a benign disorder that is usually considered a form of migraine. The headaches are often self-limited and respond to indomethacin. Coital headache is usually bilateral, throbbing, and intense. It is more common in men than in women and usually occurs just prior to orgasm. The major differential diagnosis is SAH.

L. Headache not conforming to known functional headache patterns.

Diagnostic Studies

I. LABORATORY STUDIES

In many patients, a diagnosis can be made on clinical grounds alone and treatment can be initiated without further testing. Headache is rarely the sole symptom of serious nervous system disorders. Patients with any of the historical factors discussed in the preceding section or with fever, focal signs, changes in cognition or consciousness, or stiff neck on examination should be evaluated more extensively.

II. BLOOD WORK

Occasionally, routine blood work may provide evidence of infection, anemia, or electrolyte or hormonal abnormalities that are related to headache. The ESR should be checked in all elderly patients with headache due to the possibility of giant cell arteritis. When the ESR

is not elevated, other acute phase reactants such as C-reactive protein, haptoglobin, or the platelet count may be increased.

III. IMAGING

Imaging studies are indicated when the clinical pattern suggests the presence of a secondary cause of headache.

A. Uninfused CT is commonly performed with the intent of excluding acute hemorrhage. It is faster than MRI, less expensive and less sensitive to movement artifact. MRI sequences showing susceptibility artifact, such as gradient echo imaging, are also sensitive for acute blood. Catheter angiography is still the gold standard for identifying aneurysms but MR angiography and CT angiography are alternative modalities.

B. MRI is preferable to CT for imaging some lesions in headache patients such as Chiari's malformations, neoplasm, and sinovenous thrombosis. Radiographic contrast increases the yield of CT in patients with tumor, vascular lesions, inflammatory disorders, and infection. However, there is insufficient evidence that this superiority of MRI is of clinical importance in patients with chronic recurrent headaches.

C. Imaging is unlikely to uncover a significant abnormality in patients with nonacute headache but CT or MRI may reveal abnormalities that are unrelated to the headaches. In a recent meta-analysis of individuals without neurologic symptoms undergoing brain MRI, almost 3% had incidental abnormalities. Evidence-based guidelines suggest that imaging should be considered when there is an unexplained abnormality on physical examination, if the headache is atypical or does not meet criteria for a primary headache disorder or if there is an additional risk factor such as immune deficiency.

D. A history consistent with migraine reduces the risk of abnormal imaging. In Frishberg's retrospective and prospective review of CT or MRI studies, only 0.4% of patients with migraine and a normal exam had abnormal imaging compared with 2.4% in patients with nonmigrainous headache. White matter changes are relatively common in migraineurs but if extensive, they may raise suspicion of a secondary migraine syndrome such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy or a mitochondrial disorder.

E. There are no evidence-based guidelines on the role of imaging in chronic nonmigrainous or tension-type headaches.

IV. LUMBAR PUNCTURE

A. Exclusion of SAH. CT is very sensitive to the presence of subarachnoid blood but the presence of CSF blood or xanthochromia may be diagnostic in patients with a high degree of suspicion and a negative CT.

B. Diagnosis of CNS infection. In patients with suspected encephalitis or meningitis, LP may indicate the presence of CSF pleocytosis. Patients should have an imaging procedure prior to undergoing LP except when bacterial meningitis is strongly suspected, in which case LP should be done immediately to prevent a potentially life-threatening delay in antibiotic therapy.

C. Measurement of CSF pressure. For the patient with chronic headache and signs of increased ICP, such as papilledema or small ventricles, especially in young obese women, idiopathic intracranial hypertension should always be included in the differential diagnosis. When imaging studies exclude a mass lesion, LP should be performed to confirm an elevation of CSF pressure.

D. Diagnosis of carcinomatous meningitis.

E. Cisternal taps. Cisternal puncture may increase the likelihood of diagnosing fungal or tuberculous meningitis, which may primarily affect basal meninges.

V. BIOPSY OF PATHOLOGIC MATERIAL IS INDICATED UNDER CERTAIN CIRCUMSTANCES

A. Diagnosis of giant cell arteritis. **Temporal artery biopsy** is still the gold standard for diagnosing cranial arteritis. A specimen of adequate length is necessary to avoid sampling error because of skip lesions. The risk of blindness in untreated patients is sufficient to warrant initiation of steroids when the diagnosis is considered. The incidence of positive biopsy results falls dramatically after short trials of steroids, so moving to biopsy rapidly is recommended. There is a modest increase in diagnostic yield by biopsying the contralateral temporal artery if the initial biopsy specimen is negative. Biopsy may be of value in diagnosing other arteritides, such as polyarteritis nodosa, which may involve the temporal artery. Preoperative angiography or ultrasound to select a biopsy site is rarely beneficial because arteriosclerotic changes are common in this age group and can be mistaken for arteritis.

B. Meningeal Biopsy. In patients with chronic meningitis, meningeal biopsy may help establish diagnoses such as granulomatous angiitis, sarcoidosis, or meningeal carcinomatosis.

VI. EEG

EEG is not recommended for routine evaluation of patients with headache, unless associated symptoms suggest a seizure.

Recommended Readings

Allison MC, Gallagher PJ. Temporal artery biopsy and corticosteroid treatment. *Ann Rheum Dis*. 1984;43:416–417.

Boes CJ, Matharu MS, Goadsby PJ. Benign cough headache. *Cephalalgia*. 2002;22:772–779.

Boyev LR, Miller NR, Green WR. Efficacy of unilateral versus bilateral temporal artery biopsies for the diagnosis of giant cell arteritis. *Am J Ophthalmol*. 1999;128:211–215.

Brightbill TC, Goodwin RS, Ford RG. Magnetic resonance imaging of intracranial hypotension syndrome with pathological correlation. *Headache*. 2000;40:292–299.

Clarke CE, Edwards J, Nicholt DJ, et al. Imaging results in a consecutive series of 530 new patients in the Birmingham Headache Service. *J Neurol*. 2010;257:1274–1278.

Dodick DW. Thunderclap headache. *J Neurol Neurosurg Psychiatry*. 2002;72:6–111.

Evans RW, Armon C, Frohman EM, et al. Assessment: prevention of post-lumbar puncture headaches—report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55:909–914.

Fisher CM. Late-life migraine accompaniments as a cause of unexplained transient ischemic attacks. *Can J Neurol Sci*. 1980;7:9–17.

Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. *Neurology*. 1993;43:1678–1683.

Frishberg BM. The utility of neuroimaging in the evaluation of headache in patients with normal neurologic examinations. *Neurology*. 1994;44:1191–1197.

Gorelick PB, Hier DB, Caplan LR, et al. Headache in acute cerebrovascular disease. *Neurology*. 1986;36:1445–1450.

Headache Classification Committee of the International Headache Society. The international classification of headache disorders. *Cephalalgia*. 2004;24(suppl 1):9–160.

Marcelis J, Silberstein SD. Idiopathic intracranial hypertension without papilledema. *Arch Neurol*. 1991;48:392–399.

Mathew NT, Ravishankar K, Sanin LC. Coexistence of migraine and idiopathic intracranial hypertension without papilledema. *Neurology*. 1996;46:1226–1230.

May A, Jurgens TP. Trigeminal-autonomic headaches in daily clinical practice. *Expert Rev Neurother*. 2006;6:1531–1543.

Medina JL, Diamond S. Cluster headache variant: spectrum of a new headache syndrome. *Arch Neurol*. 1981;38:705–709.

Mitchell C, Osborn RE, Grosskreutz SR. Computed tomography in the headache patient: is routine evaluation really necessary? *Headache*. 1993;33:82–86.

Morris Z, Whitely WN, Longstreth WT, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2009;339:b3016.

Pless M, Rizzo JF 3rd, Lamkin JC, et al. Concordance of bilateral temporal artery biopsy in giant cell arteritis. *J Neuroophthalmol*. 2000;20:216–218.

Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: the electroencephalogram in the evaluation of headache. *Neurology*. 1995;45:1411–1413.
Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: proposed revision to the IHS criteria. *Headache*. 1994;34:1–7.
Silberstein SD for the U.S. Headache Consortium. Practice parameter: evidence-based guidelines for migraine headache (an evidence based review). *Neurology*. 2000;55:754–762.
Tsushima Y, Endo K. MR imaging in the evaluation of chronic or recurrent headache. *Radiology*. 2005;235(2):575–579.
Vijayan N, Dreyfus PM. Post-traumatic cephalalgia. *Arch Neurol*. 1975;32:649–652.
Vijayan N, Watson C. Pericarotid syndrome. *Headache*. 1978;18:244–254.

CHAPTER 22

Approach to the Patient with Neck Pain and/or Arm Pain

Scott A. Shapiro

I. TRAUMATIC NECK PAIN WITHOUT ARM PAIN

A. Introduction. Trauma to the neck secondary to a motor vehicle accident, work-related injury, or athletic injury is a common cause of musculoskeletal neck pain. In the vast majority of patients, post-traumatic neck pain is a self-limited problem that is not serious.

B. Etiology. Straining of anterior/posterior cervical muscles and tendons is the mechanism of pain for most post-traumatic neck pain syndromes. The most common cause in clinical practice is vehicular accidents with hyperextension/flexion to the neck (whiplash). Altercations, athletic injuries (especially football), and lifting/tugging work injuries also occur.

C. Evaluation.

1. **History and physical examination.** The primary complaints are post-traumatic neck pain and neck stiffness. The paracervical muscles are tender with limitation of motion, spinous process point tenderness may be present and there may be some associated interscapular pain and headache. Complaints of patchy arm numbness are occasionally reported but the neurologic exam is normal for the vast majority of patients.
2. **Radiographs.**
   a. **Plain X-rays** rule out most fractures and ligamentous instability. In the under-40 age group, the most common finding is loss of the lordotic curve from muscle spasm. In the over-40 age group, X-rays often show degenerative changes such as narrowed disc spaces and osteophyte (bone spur) formation. The accident is not the cause of these X-ray changes but certainly these changes can predispose the patient to more pain than a normal spine.
   b. **CT scan/MRI scan.** Any clinical or radiographic evidence for acute fracture, subluxation (instability), or spinal cord injury requires a thorough evaluation including a cervical CT scan, consultation with a spine specialist and, more often than not, a cervical MRI scan.

D. Referral.

1. **First 2 to 3 weeks (medicate and wait).**
   a. **Soft collar.** Post-traumatic neck pain will usually subside on its own over a week or. A narrow soft cervical collar can be helpful in taking the weight of the head off the neck and transferring it to the shoulders. The collar should not be so tall that it forces that patient into hyperextension, which is uncomfortable.
   b. **Medication.** Over the counter nonsteroidal anti-inflammatory medication (ibuprofen) with/without acetaminophen is the ideal analgesic. Other analgesics, such as propoxyphene, codeine, or codeine analogs, are acceptable but no schedule-3 narcotics, such as oxycodone, demerol, or morphine, should be used. Muscle relaxants such as Robaxin (methocarbamol) 500 mg P.O. every 6 to 8 hours, Flexeril (cyclobenzaprine) 10 mg P.O. three times a day, or Parafon Forte (chlorzoxazone) 500 mg P.O. every 6 to 8 hours can help. Do not use benzodiazepines due to the abuse potential. In the patient whose stomach is sensitive to nonsteroidal medication, an evening dose of an H-2 receptor blocker such as cimetidine 300 to 600 mg P.O. can help prevent gastritis.
   c. **Time-off from work.** Desk-bound workers with mild to moderate neck pain can work, and most ambitious people are able to function. Heavy laborers may benefit from light duty or 1 to 2 weeks off work. Beware of patients who exhibit symptom magnification and functional overlay due for purposes of secondary gain (worker's compensation and litigation). They have the tendency to abuse time-off work. In these scenarios, early referral to a physical medicine and rehabilitation specialist who can scientifically assess for malingering may be helpful.

2. **Weeks 3 to 6 if pain still present.**
   a. **Physical therapy.** If the neck pain does not subside after 2 weeks, physical therapy—heat, ultrasound, massage, and transcutaneous electrical nerve stimulation (TENS)—is reasonable.
   b. **Pain clinic.** Trigger point injections of anesthetic/steroid can be helpful but are probably best scheduled after evaluation by a spine specialist.
3. **After 6 to 8 weeks.** When neck pain persists after 6 to 8 weeks, despite rest and therapy, and the pain remains severe enough to interfere with work or recreation, the next diagnostic test should be a cervical MRI scan to evaluate the cervical discs. Usually the study is normal or shows mild cervical disc dehydration with disc bulging. Neck pain from cervical disc dehydration can best be treated by cervical traction. Minor cervical disc bulging presenting with chronic pain, with a normal neurologic exam, is rarely sufficient indication for surgery. At this point, it is best to get the opinion of a neurosurgeon.

II. NONTRAUMATIC NECK PAIN OF ARTHRITIC ORIGIN

A. **Introduction.** Neck pain from degenerative arthritis of the neck is of epidemic proportion (60% to 80%) in the elderly population.
B. **Etiology.** Degenerative arthritis of the cervical spine occasionally manifests itself as early as the third decade of life but is much more common with increasing age. Disc dehydration and disc space narrowing with osteophyte formation is a process that occurs naturally with age. Facet arthritis also occurs. Small nerve fibers innervating the disc and facet can be involved leading to neck pain. Dural impingement by osteophytes can also produce neck pain—especially with extension or lateral gaze.
C. **Evaluation.**
1. **History and physical examination.** Nontraumatic neck pain in the over 40 age group is most often secondary to cervical degenerative arthritis. The pain is gradual in onset and initially intermittent and then becomes more constant. There can be associated occipital headache and interscapular pain. Motion, especially extension or lateral gaze, can aggravate the pain.
2. **Radiographs.** X-rays show narrowing of disc spaces with bone spur formation. At least 70% of the populations over the age of 65 have significant changes of degenerative arthritis. Regardless of how bad the X-rays look, if the patient is neurologically normal, MRI or surgery is not absolutely indicated.

D. **Referral.**
1. **Medication. (Same as for traumatic neck pain.)**
2. **Physical therapy.** Heat, ultrasound, massage, and TENS unit therapy can help.
3. **Pain clinic.** Trigger point injections can help.
4. **Alternative therapies.** Although chiropractors can help many people, we cannot advocate manipulation of the neck when obvious bone spurs exist. Neurologic catastrophes and lawsuits have occurred. Patients can seek chiropractic care at their own risk. Recently, magnets have become popular in relieving arthritic complaints with some scientific credence. Finally, oral glucosamine has been shown somewhat effective against arthritis, although its effect on cervical spondylosis remains to be determined.
5. **Spine specialists.** In the majority of patients with neck pain and no arm pain, surgery is not indicated. The removal of large osteophytes ventral to the spinal cord can improve severe neck pain, occipital headache, and actually improve the range of motion. Only an experienced spinal surgeon should make this decision based on a CT scan/MRI scan and repetitive physical exams over a period of time.

III. NECK PAIN WITH ARM PAIN (RADICULOPATHY) FROM SOFT CERVICAL DISC BULGES/HERNIATIONS

A. **Etiology.** In the under-50 age group, the most common cause will be a single-level soft cervical disc. The concept of a soft cervical disc means either an eccentric disc bulge or a free fragment herniation compressing a root. A disc consists of an inner water-laden

mucoid nuclear material and an outer fibrous annulus. The annulus can fissure, allowing the nucleus either to bulge or to herniate out. There is no osteophyte involved in the compression. The posterior longitudinal ligament extends beneath the entire spinal cord, protecting the cord from disc herniation, and so a disc herniation primarily projects laterally into the foramen, compressing the nerve only. In rare cases, sufficient force, such as in trauma, can lead to a large disc herniation, causing an acute myelopathy.

B. Anatomy. A disc is named by the bordering vertebral bodies. Thus, the disc between vertebral bodies C5 and C6 is named the C5–C6 disc. The nerve root whose number corresponds to that of a given vertebral body exits above that body's pedicle. Thus a C5–C6 disc compresses the C6 nerve root.

C. Evaluation.

1. **History.** In the classic story, there is intermittent neck pain and then severe neck pain, and arm pain develop. Rarely is this condition traumatic in origin. The pain radiates down the shoulder and into the arm. There are some dermatomal patterns of radiation that can help discern the level of herniation. Patients may complain of various combinations of suboccipital headache, interscapular pain, numbness, tingling, and weakness. The pain often awakens the patient from sleep.
2. **Physical exam.**
   a. **Neck exam.** There is posterior tenderness, especially tenderness at the spinous process near the level of involvement and paracervical tenderness. Painful limitation of motion with extension and lateral gaze to the side of arm pain is classic.
   b. **Arm exam.**
      (1) **C5 radiculopathy (C4–C5 disc herniation)** presents with pain and numbness radiating to the shoulder along with a weak deltoid muscle (shoulder abduction). Simultaneous testing of both deltoid muscles by compression on the outstretched upper arms detects minor weakness (Table 22.1). There is no true muscle stretch reflex to test.
      (2) **C6 radiculopathy (C5–C6 disc herniation).** C5–C6 disc herniation is the second most common cervical disc herniation. Pain and numbness radiate across the top of the neck and along the biceps to the lateral aspect of the forearm, and dorsal thumb and index finger. Numbness is usually more distal. A weak biceps, a reduced biceps reflex and weak wrist extension are observed.
      (3) **C7 radiculopathy (C6–C7 disc herniation).** This is the most common disc herniation. Pain radiates across the top of the neck, across the triceps, and down the posterolateral forearm to the middle finger. Numbness again is more distal. A weak triceps and reduced triceps reflex are observed.
      (4) **C8 radiculopathy (C7–T1 disc herniation)** is very uncommon. Pain and numbness radiate across the neck and down the arm to the small finger and ring finger. Wrist flexion and the intrinsic muscles of the hand are weak.
3. **Radiographic evaluation.**
   a. **Plain X-rays** provide very little help. They may show slight narrowing of the disc space involved and loss of lordosis.
   b. An **MRI scan** without contrast is the study of choice for demonstrating a cervical disc herniation (Fig. 22.1).
4. **Electromyogram (EMG) and nerve conduction velocity studies (NCVs).** An EMG for a single-level disc herniation with a radiculopathy is not absolutely necessary. It can help when other disorders, such as amyotrophic lateral sclerosis, carpal tunnel syndrome, and brachial plexopathy, need to be ruled out.

TABLE 22.1 Motor Strength Classification (0 to 5 Scale)

0, no movement
1, flicker of movement
2, able to move but not against gravity
3, able to move against gravity but offers no resistance
4, offers resistance but able to overcome or easy fatigue
5, normal

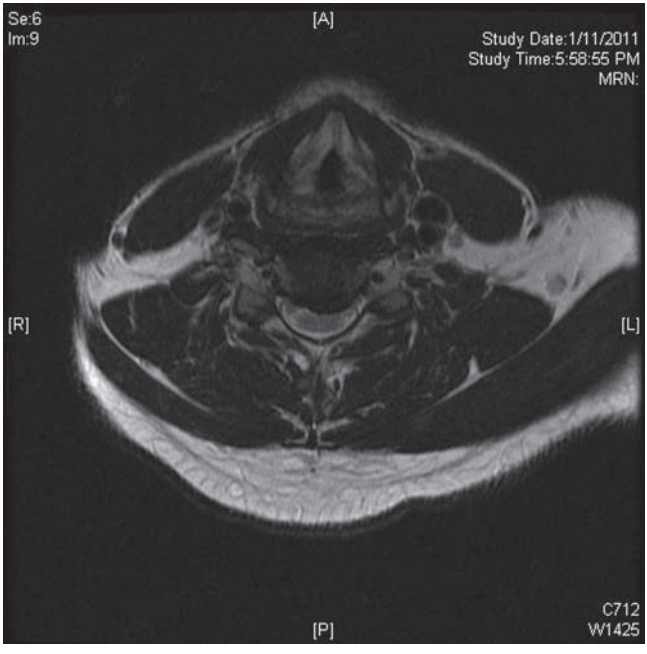


FIGURE 22.1 Axial T2-weighted MRI demonstrating a large eccentric cervical disc protrusion (C5–C6) causing impingement on the ventral aspect of the spinal cord and foraminal impingement.

D. Referral.

1. **Physical therapy.** After diagnosis by MRI, a patient with a motor strength rating of 4/5 or more (Table 22.1) can be referred for cervical traction, heat, ultrasound, massage, and a soft collar. Initially, cervical traction should be done by a physical therapist. Inform the therapist that if traction is tolerated; the patient is to be instructed in home cervical traction at 10 lb for half-an-hour every night. Approximately 60% to 80% of soft disc herniations improve to the point of resolution of the radiculopathy with traction alone within 4 to 6 weeks. Not every patient can tolerate traction.
2. **Medication.** A trial of 4-mg self-weaning methylprednisolone (Medrol) dose pack can be used early in the treatment prior to nonsteroidals with some success. Other medicines were previously discussed in the section on traumatic neck pain.
3. **Time-off from work.** Desk-type workers with mild to moderate neck/arm pain can work, and most ambitious people are able to function. Heavy laborers may benefit from light duty or 1 to 4 weeks off work. Beware of patients who exhibit symptom magnification and functional overlay for purposes of secondary gain (worker's compensation and litigation). They have the tendency to abuse time-off work. In these scenarios, early referral to a physical medicine and rehabilitation specialist who can scientifically assess for malingering may be helpful.
4. **Spine specialist.** In any patient with three-fifth strength or worse, immediate referral to a spine surgeon is indicated. The longer a root is compressed with severe weakness, the less likely strength will return to normal. If the strength remains four-fifth or better but pain persists after 3 to 6 weeks of traction, then referral to a spine surgeon is also indicated. A well-trained spine surgeon should achieve improvement of arm pain and weakness in 90% to 95% of soft cervical disc herniations.

IV. NECK PAIN WITH ARM PAIN FROM BONE SPURS (HARD DISC, CERVICAL SPONDYLOSIS)

A. Introduction. The combination of neck pain and arm pain in cervical spondylosis is also of epidemic proportions in the elderly population.

B. Etiology. Disc dehydration and narrowing leads to bone spur formation at the margins of the vertebral body. The spurs can project into the foramen or canal, compressing the nerve root or the spinal cord, or both. In addition, facet arthritis with resultant hypertrophy and ligamentous hypertrophy also narrow the spinal canal and neural foramens. With progressive age, more than one disc space is usually involved. The center of the process usually extends from C4 to C7.

C. Evaluation.

1. **History.** This condition occurs primarily in patients older than soft cervical disc herniation patients, although the two groups overlap. About 90% of patients have gradual onset of neck pain with progression to neck and arm pain. The pain radiates down the shoulder and into the arm. There are some dermatomal patterns of radiation that can help discern the level of root compression. Various complaints of suboccipital headache, interscapular pain, numbness, tingling, and weakness may also be present. The pain often wakes the patient up from sleep. About 10% of patients have asymptomatic degenerative arthritis, and then symptoms of neck pain/arm pain are often precipitated by hyperextension/flexion injuries from trauma (motor vehicle accidents.) A large percentage have multiple disc spaces involved, making it more difficult to determine which level or levels caused the radiculopathy.
2. **Physical examination.**
   a. **Neck examination.** There is posterior tenderness, especially tenderness at the spinous process near the level of involvement and paracervical tenderness. Painful limitation of motion with extension and lateral gaze to the side of arm pain is classic.
   b. **Arm examination (see Table 22.1) same as discussed in soft cervical disc section.**
   c. **Leg examination (Table 22.2).** Gait is usually normal even in the face of significant radiographic evidence of spinal cord compression. Occasionally, myelopathy is present. Early on, the gait is normal in the face of increased muscle stretch reflexes and Babinski's sign. With more severe and prolonged compression, one can observe spastic gait with bowel and bladder problems. In the most severe cases, the patient requires a cane or a walker. Rarely is it allowed to progress to wheel chair dependency.
3. **Radiographs.**
   a. **Plain X-rays** show disc space narrowing with osteophyte (bone spur) formation. Oblique films can exhibit neuroforaminal narrowing.

TABLE 22.2 Nurick Classification

Grade	Characteristic
1	Signs of spinal cord disease but normal gait
2	Slight gait abnormality not preventing full time employment
3	Gait abnormality severe enough to prevent employment or housework. Still able to ambulate independently
4	Requires a walker or someone else's help to ambulate
5	Wheelchair bound

b. **MRI scan (Fig. 22.2).** It is excellent for demonstrating nerve-root compression and cord compression from bone spurs. It does not provide as much detail about bone anatomy as the CT scan.
c. **CT scan (Fig. 22.3A, B).** It shows better bone detail than MRI, but is not as good at showing the neural structures. The two studies together are ideal for this group of patients, but this is obviously not cost effective, so MRI is the first choice.

4. **EMG and NCVs.** An EMG can be helpful in discerning which roots are most involved in patients with multi-level spondylosis.

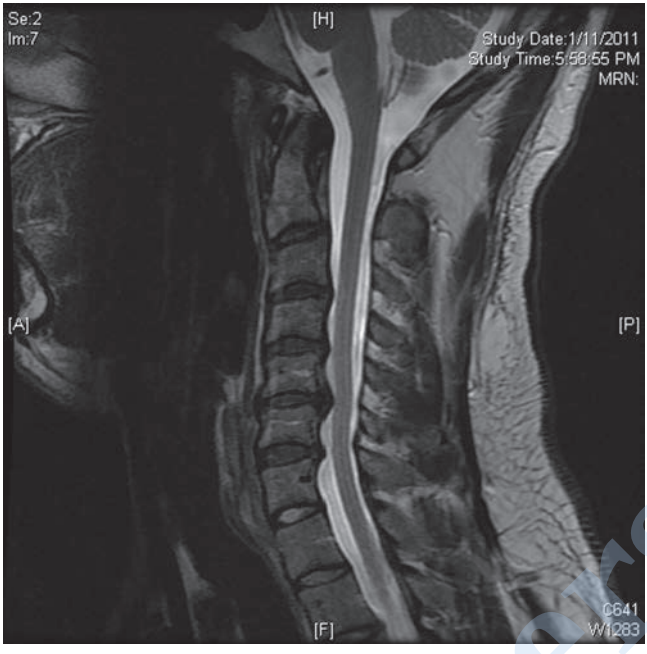


FIGURE 22.2 Sagittal MRI of the cervical spine demonstrating multiple-level spondylosis.

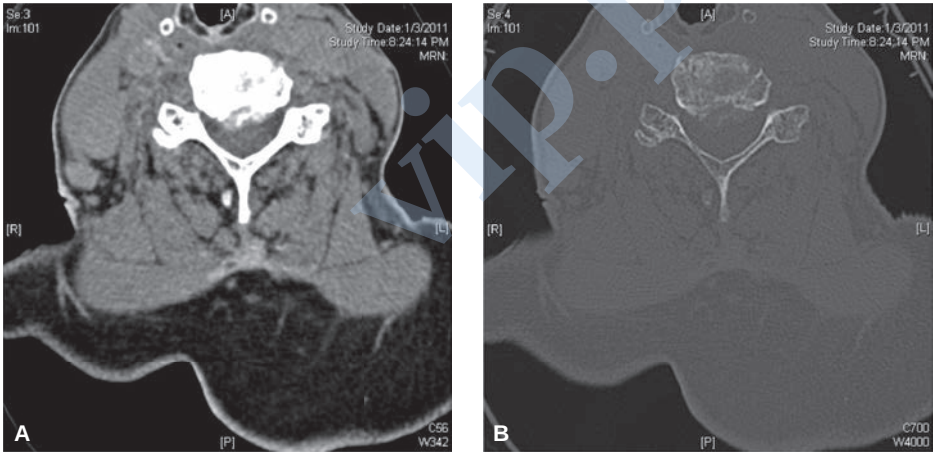


FIGURE 22.3 Axial CT with soft tissue **(A)** and bone windows **(B)** demonstrating moderate to severe central canal stenosis secondary to an eccentric disc protrusion (C5–C6) as well as osteophyte with foraminal stenosis.

D. Referral.

Medication. As discussed in previous medication sections.

1. **Soft cervical collar.**
2. **Physical therapy.** Heat, ultrasound, massage, traction, and TENS can reduce the symptoms. Approximately 20% of the radiculopathies (arm pain/strength) can be successfully improved with medicine and therapy alone for many years. The majority of patients have some pain with persistent mild weakness (if any weakness is present). Rarely does myelopathy develop in this group of patients.
3. **Spine specialist.** Surgery for cervical spondylotic radiculopathy is almost always elective. Results of surgery are much better for single-level disease than for multi-level disease, especially for neck pain. Arm motor strength of three-fifth or worse and any evidence for myelopathy is an indication for immediate referral to a spine surgeon. The anterior approach is superior to the posterior approach if bone spurs project under the entire spinal cord. Surgery helps the radiculopathy in 90% to 95% of both single-level disease and multi-level disease patients, but neck pain improves in only 70% to 75% of multi-level disease patients. Complete relief of radicular pain occurs in approximately 60% to 80% of cases. There is no age cutoff for surgery as long as patient is in reasonable medical condition. The elderly tolerate surgery very well with minimal morbidity. If a myelopathy is present with gait abnormality and an aggressive decompression is performed, an improvement of one grade on Nurick's scale (see Table 22.2) can be expected in 70% to 80% of patients. Duration of symptoms is very important for patients with gait problems. Thus early referral is indicated.

V. NECK PAIN WITH/WITHOUT ARM PAIN DUE TO METASTATIC CANCER OF THE CERVICAL SPINE

A. Introduction. As patients live longer with various malignancies, the number of patients who present with spine metastases also increases. The tumors that most commonly involve the spine are lung cancer, breast cancer, prostate cancer, lymphomas, and multiple myeloma. As many as 20% of these tumors will develop symptomatic spinal involvement. In approximately 10% of patients, metastatic spinal involvement will be the mode of presentation with no known primary tumor.

B. Evaluation.

1. **History and physical examination.** Both primary and metastatic tumors of the spine initially present with pain that is often worse at night. The pain continues to worsen over a very short period, and then neurologic symptoms, such as radiculopathy and myelopathy, develop fairly quickly. It is best to make the diagnosis when neurologic symptoms are minimal.
2. **Radiographs.**
   a. **Plain X-rays** can show destruction of the vertebral bodies and pedicles (Fig. 22.4). Pathologic compression fractures and lytic pedicles are very common. The sensitivity of plain X-rays is approximately 60%.
   b. **Bone scans** are very sensitive—approaching 100%—in showing spine metastases, including asymptomatic areas with no destruction.
   c. **MRI scans** are ideal for delineating canal involvement, cord compression, and surgical feasibility.

C. Referral.

1. **Radiation therapy.** Diffuse disease involving large amounts of the spine is treated primarily with steroids and radiation therapy. Radiation is usually reserved for the symptomatic areas only. Dexamethasone 2 to 20 mg P.O. every 6 hours can be quite helpful in improving pain and neurologic symptoms.
2. **Surgery.** Early referral to a spine surgeon is warranted following diagnosis regardless of the neurologic exam. If surgery is indicated, it is often best to perform it prior to radiation therapy, because this reduces the wound complication rate. In the face of a cervical myelopathy resulting from diffuse canal involvement and cord compression, a laminectomy can be performed. Patients with lung cancer do very poorly and it is hard to justify

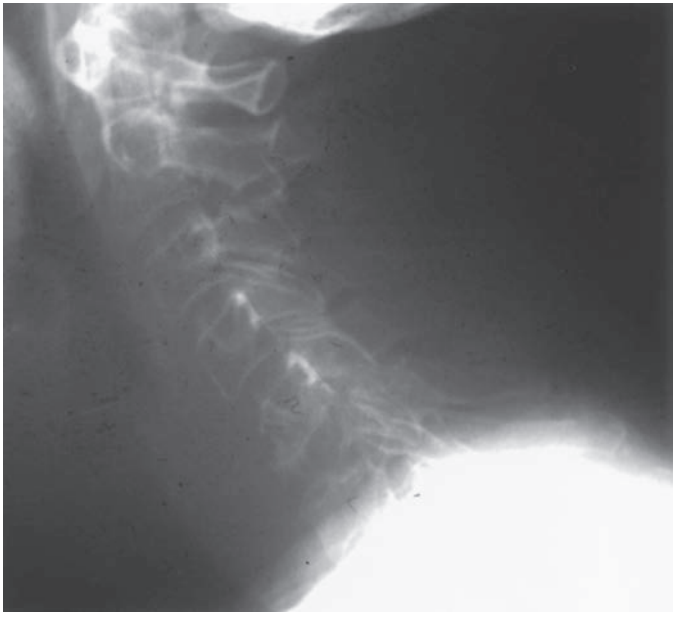


FIGURE 22.4 Lateral radiograph demonstrating lytic destruction of the C6 vertebral body.

surgery scientifically for metastatic lung cancer unless there is no primary disease the spine disease is the only systemic metastasis. Other tumors do better, but a good rule is 30% to 50% of all tumors are improved by laminectomy with a 10% mortality rate. Isolated vertebral body disease can be resected from an anterior approach—especially in well-controlled breast cancer, prostate cancer, lymphoma, and renal cell cancer with excellent long-term results that are superior to radiation alone.

VI. MISCELLANEOUS NECK PAIN WITH/WITHOUT ARM PAIN

A. Rheumatoid arthritis.

1. **Etiology.** Rheumatoid arthritis can affect the C1–C2 articulation leading to erosion of the odontoid process and transverse atlantal ligament, which leads to C1–C2 instability and cord compression from the developing panus.
2. **Evaluation.**
   a. **History and physical examination.** Severe neck pain is usually followed by arm pain and a progressive myelopathy.
   b. **Radiographs.** Plain X-rays and MRI scans are best for showing erosion of the odontoid process with subsequent instability (Fig. 22.5).
3. **Referral and therapy.** Place a soft collar and refer immediately to a spine surgeon. Posterior C1–C2 fusion with transarticular screws is ideal for the problem; occasionally an anterior transoral odontoidectomy is required. These treatments are not without risk and must be individualized.

B. Discitis/osteomyelitis.

1. **Introduction.** Bacterial discitis/osteomyelitis is extremely uncommon in the cervical spine and fever may not be present.
2. **Evaluation.**
   a. **History and physical examination.** There may be a prior history of skin infection, urinary tract infection, or pulmonary infection. Iatrogenic discitis/osteomyelitis

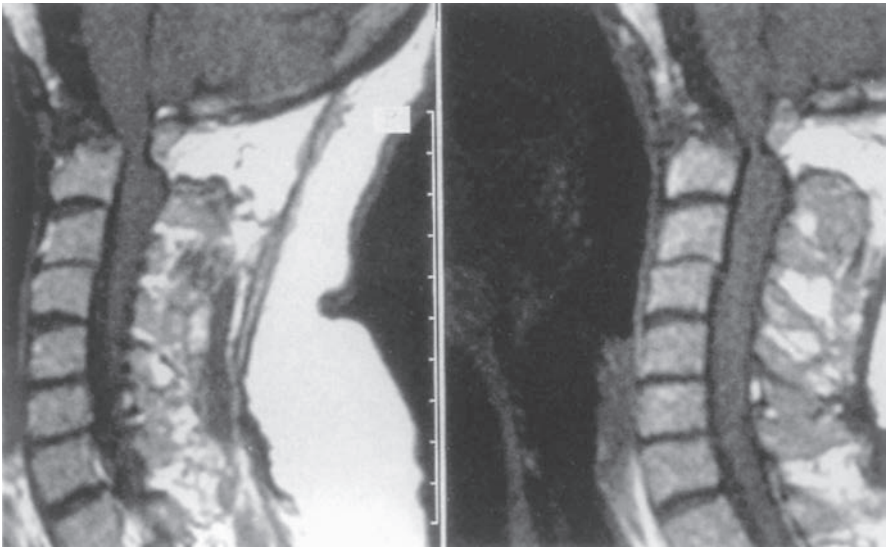


FIGURE 22.5 **Left** and **right:** Sagittal MRI scans in rheumatoid arthritis demonstrating destruction of the dens with compression of the medulla and spinal cord at the cranio-cervical junction.

complicating cervical spine surgery is known to occur. Perhaps the most common cause in urban settings is a history of intravenous drug abuse. Progressive neck pain with a rapidly progressive myelopathy is the usual presentation.

b. **Radiographs.** Plain X-rays show disc space collapse with erosion of the bordering vertebral bodies. MRI shows epidural spinal cord compression from kyphosis or epidural abscess.

3. **Referral.** The patient should be immediately referred to either a spine specialist or an infectious disease specialist. An immediate radiology-directed needle biopsy/culture or open biopsy culture, and administration of intravenous bactericidal antibiotics for at least 6 weeks, are indicated. Surgical debridement and decompression are performed for severe kyphosis and neurologic problems.

Recommended Readings

Bracken M, Shephard M, Collins W, et al. Methylprednisolone or naloxone treatment after acute spinal cord injury: 1 year follow up data. Results of the second national acute spinal cord injury study. *J Neurosurg*. 1992;76:23–31.

DePalma A, Rothman R, Levitt R, et al. The natural history of severe cervical disc degeneration. *Acta Orthop Scand*. 1972;43:392–396.

Melhem E. Technical challenges in MR imaging of the cervical spine and cord. Magn Reson Imaging Clin N Am. 2000;8:435–452.

Modic M, Masaryk T, Ross J, eds. *Magnetic Resonance Imaging of the Spine*. Chicago, IL: Year Book Medical Publishers; 1989.

Patchell R, Tibbs P, Regine W, et al: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomized trial. *Lancet*. 2005;366:643–648.

Pellicci P, Ranawat C, Tsairis P, et al. A prospective study of the progression of rheumatoid arthritis of the cervical spine. *J Bone Joint Surg Am*. 1981;63:342–350.

Ropper A, Samuels M. *Adams and Victor's Principles of Neurology*. 9th ed. New York, NY: McGraw Hill Inc; 2009.

Rothman R, Simeone F, eds. *The Spine*. Vol 1 & 2. Philadelphia, PA: WB Saunders & Co; 1992.

Shapiro S. Banked fibula, locking cervical plate following anterior cervical discectomy. *J Neurosurg*. 1996;84:161–165.

Shapiro S. Spinal instrumentation with a low complication rate. *Surg Neurol*. 1997;48:566–574.

Wilkins R, Rengachary S, eds. *Neurosurgery*. Vol 1–3. New York, NY: McGraw-Hill Book Co; 1996.

Wong D, Fornasier V, MacNab I. Spinal metastases: the obvious, the occult and the imposters. *Spine*. 1990;15:1–4.

CHAPTER

23 Approach to the Patient with Low Back Pain, Lumbosacral Radiculopathy, and Lumbar Stenosis

Paul B. Nelson

A. Acute low back pain. Back pain is extremely common. Most adults can remember at least one episode of back pain sometime in their lives. Approximately 50% of working adults have back pain at least 1 day per year. Back pain has become one of the most expensive health care problems and has become a leading cause of disability among persons younger than 45 years. The estimated annual cost of medical care of patients with low back pain is more than 8 billion dollars.

B. Lumbar disc disease with sciatica. Patients with back and leg pain (sciatica) most likely have nerve-root compression secondary to rupture of a lumbar disc. Although it occurs occasionally in the pediatric and geriatric age groups, a ruptured disc generally occurs in the third to fifth decades of life. Approximately 90% of cases of rupture of lumbar discs occur between L4–5 and L5–S1; 5% occur at L3–4. The incidence of disc rupture is the same among men and women.

C. Lumbar spinal stenosis is any type of narrowing of the spinal canal, lateral recess, or intervertebral foramina secondary to congenital causes, disc degeneration, bony hypertrophy, ligamentous hypertrophy, or spondylolisthesis. Because it is caused primarily by degenerative change, the disease seldom occurs before the fifth decade of life. The mean age of patients undergoing operative procedures for lumbar stenosis is the sixth decade, although it sometimes occurs in the seventh and eighth decades. Lumbar stenosis is most commonly observed at L4–5 and L3–4.

I. ETIOLOGY

A. Acute low back pain. Most low back is due to mechanical abnormalities (muscle strain, ligamentous injury, annular tears, etc.). With the disorder being so common and so often mechanical in nature, back pain must be considered a normal part of aging. Degenerative changes in the spine begin in the second decade of life and are extremely common by the fifth decade.

A small percentage of patients have structural abnormalities that account for low back pain. Spondylolisthesis, which is a forward slipping of one vertebral body over another, is caused by defects in the pars interarticularis (spondylolysis) in the younger age group and by degenerative changes in the older age group. Lumbar scoliosis, which is a lateral deformity of the spine, usually is caused by degenerative disease. Primary or metastatic bone tumors or infections of the disc or epidural space are much less common causes of back pain.

B. Lumbar disc disease with sciatica. A lumbar disc acts as an articulation between the vertebrae and as a cushion. It is composed of a cartilaginous end plate and an outer annulus that surrounds the nucleus. Degenerative changes begin in the disc by the late 20s and are common by the fourth decade. Alterations in the lumbar disc from age alone and major or minor trauma can cause an intervertebral disc to rupture. The disc most commonly ruptures in a posterolateral direction. Disc extrusions and some protrusions can cause nerve-root or, less frequently, cauda equina compression.

C. Lumbar spinal stenosis. Except in patients born with short pedicles, spinal stenosis is secondary to degenerative changes and many years of repetitive trauma. With age, the disc loses its water content and stops functioning as a cushion. There is increased stress on the bony vertebrae, the ligaments, and the facets. There is increased mobility of the vertebral bodies, ballooning of the disc, and hypertrophy of the ligaments. All these changes can cause narrowing of the lumbar canal. Absolute spinal stenosis is defined as a midsagittal diameter of 10 mm or less. A normal lumbar canal is 15 to 25 mm in diameter.

II. CLINICAL MANIFESTATIONS AND EVALUATION

A. History.

1. **Acute low back pain.** The history interview must determine whether the back pain is mechanical or associated with a more serious problem. It must also determine whether there are any "red flags" that suggest more serious causes of the back disorder (Table 23.1). Symptoms and histories that should alert the physician that there may be a disorder more serious than regular mechanical low back pain include night pain, fever, severe back spasms, leg pain, leg weakness, leg numbness, bladder or bowel dysfunction, major trauma, minor trauma in a patient with osteoporosis, weight loss, lethargy, back pain in a child, history of previous bacterial infection, history of carcinoma, history of intravenous drug use, and a worker's compensation or legal claim.
2. **Lumbar disc disease with sciatica.** A patient with sciatica usually has a history of back pain for several days before the development of leg pain. In L4–5 and L5–S1 disc disease, the back pain actually may be somewhat relieved as the patient goes on to have burning discomfort in the buttocks and unilateral pain in the posterolateral aspects of both the upper and lower leg. There may also be numbness or tingling in a portion of the foot or toes. The less common L3–4 disc disease can cause pain in the groin and anterior aspects of the thigh and upper leg. The history occasionally is one of severe sciatic pain from the onset. Bilateral leg pain and bladder or bowel dysfunction suggest cauda equina compression from a large midline disc extrusion.
3. **Lumbar spinal stenosis.** In spinal stenosis, the history is more important than the examination. The patient typically reports back and leg discomfort, numbness, or heaviness with standing or walking. Symptoms improve with rest or forward bending. The leg symptoms usually are asymmetric. Occasional patients have true sciatica.

B. Physical examination.

1. **Acute low back pain.** Examination of a patient with acute low back pain should begin with inspection and palpation of the low back. Paravertebral muscle spasms may be present. In most cases of mechanical back pain, straight-leg-raise testing causes back pain only. Straight-leg-raise testing that causes back and leg pain suggest root or cauda equina compression. The neurologic examination should include walking on the heels and toes, squatting, and individual testing of the foot and toe dorsiflexors and plantarflexors, the quadriceps, and the iliopsoas muscles. The general examination should include palpation of the abdomen, to rule out an abdominal aortic aneurysm, and a rectal examination.
2. **Lumbar disc disease with sciatica.** The patient walks in a slow, deliberate manner with slight forward tilt of the trunk. Paravertebral muscle tightness can cause decreased range of motion of the back, and asymmetric muscle tightness can cause associated scoliosis. The patient prefers to stand or lie rather than sit. The best position usually is lying on the unaffected side with the affected leg slightly bent at the knee and hip. The pain frequently is worsened by Valsalva's maneuver.

TABLE 23.1 "Red Flags" That Suggest Serious Causes of Low Back Pain

Symptoms, History	Possible Diagnosis
Night pain	Tumor
Fever, history of recent bacterial infection or intravenous drug use, severe back spasms	Diskitis and epidural abscess
Leg pain	Nerve-root compression
Bilateral lower extremity weakness or numbness, bladder or bowel dysfunction	Cauda equina or conus compression
Major trauma	Fracture, dislocation
Minor trauma in a patient with osteoporosis	Compression fracture
History of carcinoma	Metastatic disease
Systemic symptoms such as fever, weight loss	Multiple myeloma
Back pain in a child	Tumor, tethered cord
Worker's compensation or legal claim	Secondary gain

a. **Straight-leg-raise testing** is important in the diagnosis of lumbar disc disease. The patient is in a supine position with the knee extended and the ankle plantar flexed. The examiner raises the leg slowly. Normally, the leg can be raised to 90° without discomfort or with slight tightness in the hamstring. When the nerve root is compressed by a ruptured disc, the straight leg raise is limited and causes back and leg pain. It worsens with dorsiflexion of the foot. In most cases, the result of the straight-leg-raise test is positive only on the side of the disc rupture. If lifting the leg without symptoms causes pain in the leg with symptoms, one must consider disc rupture in the axilla of the nerve root.

b. **Motor testing** is directed at the nerve roots most commonly affected. Compression of the L5 nerve root can cause foot and great toe dorsiflexion weakness (tibialis anterior and extensor hallucis longus). When the compression is severe, the patient may have foot drop. Compression of the S1 nerve root can cause plantar flexion weakness. This is difficult to detect at the bedside and is best tested by having the patient do toe raises one leg at a time. Weakness at L4 can cause quadriceps weakness. The patient may have the sensation that the leg is giving way. Disease of the L3–4 disc decreases the knee reflex, and disease of the L5–S1 disc decreases the ankle reflex.

c. **Sensory loss** resulting from a disc rupture seldom occurs in a dermatomal pattern. Rupture of the L5–S1 disc can cause relative hypalgesia in the bottom of the foot, lateral aspect of the foot, and little toe. Rupture of the L4–5 disc can cause relative hypalgesia in the dorsum of the foot and great toe. Rupture of the L3–4 disc can cause sensory loss in the anterior thigh and shin.

3. **Lumbar spinal stenosis.** Findings at neurologic examination of the lower extremities may be relatively unremarkable at rest. One occasionally may find evidence of mild nerve-root dysfunction such as L5 numbness and weakness.

III. DIFFERENTIAL DIAGNOSIS

A. Acute low back pain with and without sciatica.

1. Lumbosacral sprain
2. Degenerative arthritis
3. Fracture
4. Metastatic disease
5. Primary bone tumor
6. Diskitis
7. Epidural abscess
8. Ankylosing spondylitis
9. Paget's disease
10. Tethered spinal cord
11. Spondylolisthesis
12. Conversion reaction

B. Lumbar spinal stenosis.

1. **Peripheral vascular disease.** Arterial vascular insufficiency can cause leg discomfort during walking but is relieved by simply stopping rather than bending forward or sitting.
2. **Degenerative hip disease** can cause limitation of standing and walking. The pain usually comes on with any type of weight bearing. Examination reveals a decreased range of motion of the hip, and hip rotation may exacerbate the discomfort. The pain associated with degenerative hip disease is most likely to be located in the proximal hip, thigh, and knee.

IV. DIAGNOSTIC APPROACH

A. Acute low back pain. In the absence of red flags that suggest a more serious disorder, most testing should be delayed for 4 weeks. If the patient does not respond to conservative treatment in 4 weeks, however, the following studies may be considered.

1. Lumbosacral radiographs of the spine.
2. MRI.
3. CT scan if MRI is not available or contraindicated, or if the patient is claustrophobic. CT should include L3–4, L4–5, and L5–S1.
4. Lumbosacral myelography and postmyelography CT seldom are needed unless it is impossible to perform MRI.
5. Laboratory tests include complete blood cell count with differential and erythrocyte sedimentation rate.
6. A bone scan can be done, especially if there is a history of carcinoma.
7. Occasionally a discogram may be done in a patient with refracting back pain, a degenerative disc and no response to extensive conservative therapy.

B. Lumbar disc disease with sciatica. Few tests are needed in the first 4 weeks if the signs and symptoms are mild to moderate. Severe sciatica and sciatica associated with marked neurologic deficits and weakness of bladder and bowel movements should be evaluated earlier. The presence of a disc rupture on an imaging study does not necessarily imply nerve-root dysfunction. Approximately 75% of adult patients with symptoms have disc bulges or protrusions. Most severe sciatica is associated with disc extrusion.

1. Plain lumbosacral radiographs of the spine should be performed.
2. MRI is the procedure of choice for evaluating a lumbar disc rupture. L5–S1 disc extrusion causing severe right Sl nerve-root compression is shown in Figure 23.1.
3. CT may be used if the patient is unable to tolerate MRI.
4. Myelography and postmyelography CT can be used occasionally if MRI and CT do not provide enough information for a diagnosis.
5. Electromyography and nerve conduction velocity studies may be helpful if the signs and symptoms do not correlate well with the MRI or CT findings and if one suspects a peripheral nerve problem.

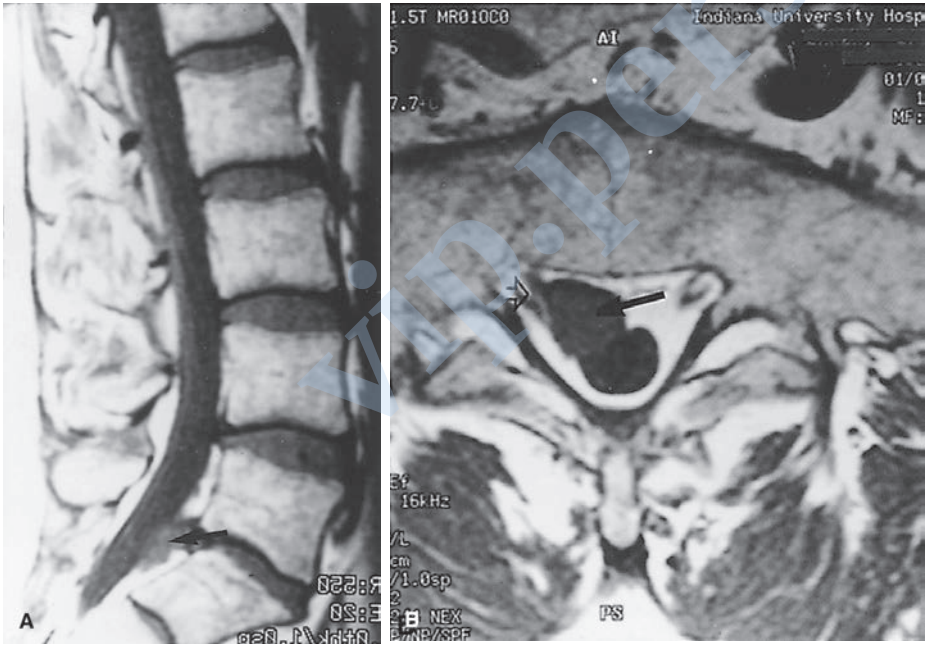


FIGURE 23.1 **A:** T1-weighted sagittal MRI shows a lumbar disc extrusion at L5–S1 that has gone down the lumbosacral canal (*arrow*). **B:** T2-weighted axial MRI shows a large, extruded L5–S1 disc fragment (*solid arrow*) compressing the right S1 nerve-root (*open arrow*).

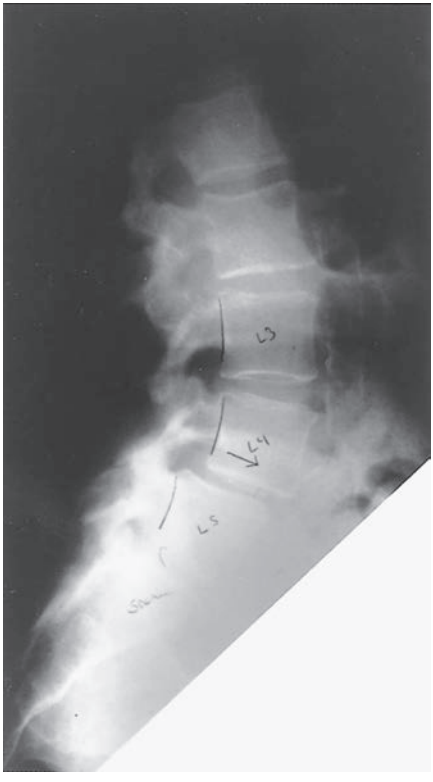


FIGURE 23.2 Lateral plain radiograph of the lumbosacral spine shows spondylolisthesis of L4 on L5.

C. Lumbar spinal stenosis. Unless the symptoms are severe, testing may not be done in the early stages of spinal stenosis. A patient who seeks medical therapy for spinal stenosis usually has a walking tolerance of <1 to 2 blocks and a standing tolerance of 20 minutes or less.

1. **Plain radiographs of the lumbosacral spine** are indicated to assess the degree of degenerative change and bone density. Flexion–extension lateral views are needed to detect degenerative spondylolisthesis (Fig. 23.2). Degenerative spondylolisthesis frequently is associated with spinal stenosis.
2. An **MRI** is the best study for evaluating the number of levels involved and the severity of the spinal stenosis. Figure 23.3 is an MRI that shows severe stenosis at L4–5.
3. **CT** can be used if MRI is not available, but CT does not show the complete lumbar spine and has poorer resolution.
4. A **bone scan** should be obtained if there is a history of malignant disease.
5. **Radiographs of the hip** are needed if there is decreased range of motion of the hip or pain with rotation of the hip.
6. **Laboratory tests.** Complete blood cell count and differential and erythrocyte sedimentation rate should be obtained and possibly serum and urine protein electrophoresis performed if there are systemic symptoms. A prostatic specific antigen assay should be performed for male patients older than 50 years.
7. **Arterial Doppler ultrasonography** should be performed if the patient has diminished or absent peripheral pulses.

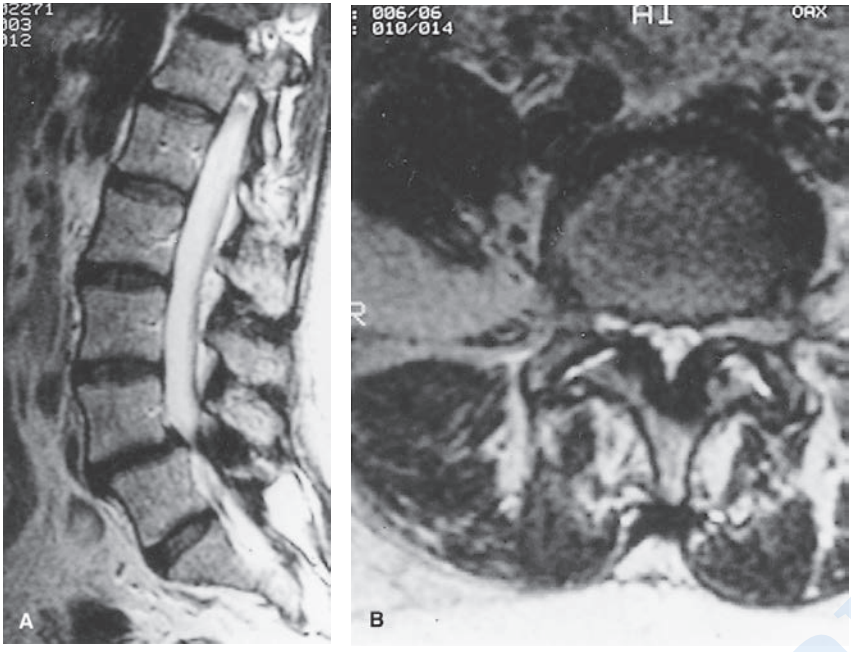


FIGURE 23.3 **A:** T2-weighted sagittal MRI shows segmental stenosis at L4–5. **B:** Axial T2-weighted MRI shows severe stenosis at L4–5. There is marked facet and ligamentous hypertrophy.

V. TREATMENT

A. Acute low back pain. Approximately 90% of patients with acute low back pain recover within 1 month. Treatment is as follows:

1. Restriction of patient activities as tolerated.
2. Acetaminophen.
3. Nonsteroidal anti-inflammatory drugs (NSAIDs).
4. Opioids, but for no longer than 2 weeks.
5. Short course of steroids (3 to 5 days).
6. Muscle relaxants.
7. Heat.
8. Limit lifting to 20 lb (9 kg) for moderate to severe back pain. Activity restrictions at work should seldom be extended beyond 3 months.
9. Surgery may be considered if the back pain is associated with a more serious problem (Table 23.1). Rarely surgery is done for refractory back pain that is associated with a degenerative disc, a positive discogram of the level of the degenerative disc, and no response to conservative therapy.

B. Lumbar disc disease with sciatica. The initial management of sciatica is similar to that of acute low back pain. At least one half of patients with sciatica improve within 1 month.

1. Two to four days of rest with gradual return to normal activities.
2. Acetaminophen.
3. NSAIDs.
4. Short course of opioids (no more than 2 weeks).
5. Short course of steroids (3 to 5 days).
6. Muscle relaxants.
7. Heat.

8. Limit lifting to 20 lb (9 kg). Try to keep work-related activity restrictions to no more than 3 months.
9. Surgery for lumbar disc disease should be considered for patients with severe pain that do not respond to conservative therapy, patients with significant weakness such as a foot drop, and a patient with bladder or bowel dysfunction. Surgery should be considered in a more urgent basis if there is significant cauda equina compression. Conservative therapy can be tried for a longer period of time when you are dealing with primarily nerve-root compression.

   There has been an increased interest using minimally invasive techniques when surgical intervention is required. Some surgeons have made use of a tubular retractor systems when performing microdiscectomies.

C. Lumbar spinal stenosis.

1. **Conservative therapy** requires that patients be taught to live within the limits of their walking and standing tolerances. They need to realize that they should get off their feet, if possible, when symptoms occur. Patient with severe limitation of walking may benefit from the use of license plates for persons with disabilities. Patients with degenerative spondylolisthesis may benefit from lumbosacral support. Flexion exercises should be considered.
2. **Surgical treatment** should be considered only if the patient's condition is medically stable and the patient can no longer live with his or her degree of spinal claudication. Patients with true sciatica that does not respond to conservative therapy also can be considered for surgery. Surgical procedures that can be considered include lumbar laminectomy, lateral recess decompression, and spinal fusion. Seldom is surgery for spinal stenosis necessary in the first 3 months of symptoms. In most cases, the patient has symptoms for 12 to 18 months. Minimally invasive techniques are now also available for both lumbar decompression and lumbar fusion procedures.

VI. SURGICAL REFERRAL

A. Severe and disabling sciatica.
B. Neurologic deficits such as foot drop or bladder and bowel disturbance.
C. Poor response to at least 4 weeks of conservative therapy.
D. Other red flags (Table 23.1).

Recommended Readings

Clinical Practice Guidelines, Acute Low Back Problems in Adults: Assessment and Treatment. Washington, DC: U.S. Department of Health and Human Services; December 1994. AHCPR publication no. 95-0643.

Foley KT, Smith MM. Microendoscopic discectomy. *Tech Neurosurg*. 1997;3:301–307.

Frymoyer JW. *The Adult Spine: Principles and Practice*. New York, NY: Raven Press; 1991.

Jensen MC, Brant-Zawadzki MN, Obuchowski N, et al. Magnetic resonance imaging of the lumbar spine in people without back pain. *N Engl J Med*. 1994;331:69–73.

Malmivaara A. The treatment of low back pain-bed rest, exercise, or ordinary activity? *N Engl J Med*. 1995;332:351–355.

McCafferty R, Khoo L, Perez-Cruet M. Percutaneous pedicle screw fixation of the lumbar spine using the PathFinder system. *Surg Tech (Lumbar Spine)*. 2006;34:591–614.

Mimran R, Perez-Curet M, Fessler R, et al. Endoscopic lumbar laminectomy for stenosis. *Surg Tech (Lumbar Spine)*. 2006;31:569–582.

Mixter WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. *N Engl J Med*. 1934;211:210–215.

Palmer S, Turner R, Palmer R. Bilateral decompression of lumbar spinal stenosis involving a unilateral approach with microscope and tubular retractor system. *J Neurosurg (Spine 2)*. 2002;97:213–217.

Perez-Cruet M. Percutaneous pedicle screw placement for spinal instrumentation. *Surg Tech (Lumbar Spine)*. 2006;32:583–590.

Rockman RH, Simeone FA. *The Spine*. Philadelphia, PA: WB Saunders; 1992.

Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonsurgical therapy for lumbar spinal stenosis. *N Engl J Med*. 2008;358:794–810.

CHAPTER 24

Approach to the Patient with Upper Extremity Pain, Paresthesias, and Entrapment Neuropathies

Mark A. Ross

Upper extremity (UE) pain and **paresthesias** are common clinical complaints that often accompany reversible peripheral nervous system (PNS) or musculoskeletal (MSK) disorders. Common PNS disorders causing these symptoms include cervical radiculopathy, brachial plexopathy, and peripheral nerve entrapment syndromes (mononeuropathies). Muscle weakness and atrophy may complicate these PNS disorders but typically do not occur with MSK disorders. The location of symptoms and signs of these PNS disorders usually reflects PNS anatomy and thus helps to suggest the diagnosis. Electrodiagnostic studies (EDS) are regularly used to clarify a specific diagnosis. The causes of UE complaints can be determined by integrating clinical history, physical findings, and diagnostic study results.

I. DIFFERENTIAL DIAGNOSIS AND ETIOLOGY

Differential diagnosis and etiology of UE pain (see Table 24.1).

II. EVALUATION

A. History.

1. **Symptoms.** The patient's description of symptoms should be obtained. Clarification of reported symptoms is helpful as patients may misuse terms, for example, saying weakness to describe numbness. The examiner should inquire about symptoms in the unaffected UE and legs, as well as performing a general review of systems to address the possibility of a generalized process or a systemic disorder.
   a. **Sensory symptoms.**
      (1) **Pain.** Pain descriptions are never pathognomonic of specific disorders. Tingling or radiating pain suggests a peripheral nerve, plexus, or root disorder, whereas dull, aching, nonradiating pain is typical of MSK disorders. Exceptions to this rule occur frequently. Acute onset of excruciating pain in the shoulder or arm is common with idiopathic brachial plexopathy. Pain radiating from the neck to the arm or hand suggests radiculopathy. The pain location may suggest the root involved—for example, lateral arm (C5), lateral forearm or thumb (C6), middle finger (C7), or medial hand and forearm (C8). Pain localized to the shoulder may result from MSK disorders, such as bicipital tendinitis, rotator cuff injury, and adhesive capsulitis, or from PNS disorders, such as C5 radiculopathy, brachial plexopathy, or entrapment of the suprascapular or dorsal scapular nerves (DSNs). Pain radiating distant from the site of pathology may belie the location—for example, carpal tunnel syndrome (CTS) occasionally manifests as forearm or shoulder pain. Forearm pain may occur with C6 radiculopathy, plexopathy, or nerve entrapment in the forearm. Pain involving specific digits may help localization. Pain involving the thumb, index finger, or middle finger suggests a median mononeuropathy, a C6 or C7 radiculopathy, or middle brachial plexus disorder. Pain involving the ring and little fingers suggests an ulnar mononeuropathy, a lower plexus disorder, or C8–T1 radiculopathy. Digital pain may also result from local MSK disorders—for example, arthritis. Bizarre descriptions of pain are typical of psychological or functional disorders.

TABLE 24.1 Differential Diagnosis and Etiology of UE Pain

Disorder	Common Etiologies
PNS disorders	
Radiculopathy	Root compression (disk and bone), trauma
Brachial plexopathy	Idiopathic, trauma, tumor, radiation, compressive (TOS)
Mononeuropathy	
Suprascapular n.	Trauma, IBP
Dorsal scapular n.	Trauma, IBP
Long thoracic n.	Trauma, IBP
Musculocutaneous n.	Trauma, IBP
Median n.	
Anterior interosseous n.	Compression, trauma
Pronator teres syndrome	Compression, trauma
CTS	Compression
Ulnar n.	
Cubital tunnel syndrome	Compression, trauma
Guyon's canal	Compression, trauma
Radial n.	
Spiral groove	Compression, trauma
Posterior interosseous	Compression, trauma
Superficial radial	Compression, trauma
MSK disorders	
Rotator cuff injury	Overuse, trauma
Biceps tendinitis	Overuse, trauma
Adhesive capsulitis	Immobility, shoulder weakness
Lateral epicondylitis	Overuse, trauma

Abbreviations: IBP, idiopathic brachial plexopathy; n. nerve.

(2) **Paresthesias and sensory loss.** Paresthesias are spontaneous sensations originating from nerve fibers, which patients describe as "tingling" or "pins and needles." Sensory loss indicates absence of normal sensation, which patients may describe as "numbness" or "like Novocain." Paresthesias and sensory loss may occur together or independently, and either suggests that PNS disease is more likely than an MSK disorder. The distribution of paresthesias or sensory loss helps localize a nerve disorder. However, patients may report a distribution of sensory symptoms that varies from the precise anatomic distribution of an affected nerve or nerve root. Patients with CTS may complain of sensory symptoms in any of the first three hand digits and often report the entire hand is numb. Thus, failure of sensory symptoms to localize precisely to a specific nerve or nerve-root distribution should not exclude these disorders. The differential diagnosis of paresthesias and sensory loss should include CNS disease, especially when pain is absent. Intermittent paresthesias also occur in normal individuals, usually related to a specific activity or limb position resulting in nerve compression, stretch, or irritation. Thus, paresthesias in isolation do not always indicate a pathologic state.

b. **Motor symptoms.** Patients complaining of weakness should be asked to describe specific activities that cause difficulty. Impaired fine motor skills—for example, buttoning buttons—indicate distal muscle weakness and suggest involvement of C8 or T1 roots, lower plexus, or nerves supplying hand muscles (median or ulnar nerves). Difficulty with arm and shoulder movements indicates proximal muscle weakness, suggesting involvement of the C5 or C6 roots, upper plexus, or nerves supplying proximal muscles (e.g., long thoracic, suprascapular, or axillary nerves). Patients with pain or sensory loss may misconstrue impaired motor performance as weakness. This possibility may be clarified during the exam or by asking the patient to state which factor chiefly limits physical performance. CNS disorders can also produce weakness of either the proximal or distal musculature.

2. **Onset and precipitating factors.** The history should address specific activities the patient participated with during or just preceding the onset of symptoms and whether or not physical activity exacerbates the symptoms.
   a. **Physical activities.** Some physical activities may predispose to specific PNS disorders. Heavy lifting may precipitate cervical disk herniation and resultant radiculopathy. Head turning often exacerbates pain or paresthesias associated with radiculopathy. Arm abduction or shoulder rotation exacerbates the pain of MSK shoulder disorders and also the pain associated with brachial plexopathy. Repetitive flexion and extension movements of the elbow or sustained elbow flexion may predispose to ulnar mononeuropathy at the elbow (cubital tunnel syndrome). Repetitive flexion and extension movements at the wrist or fingers may predispose to median mononeuropathy within the carpal tunnel (CTS). Repetitive pronation and supination may lead to hypertrophy of the pronator teres muscle and median nerve entrapment in the forearm (pronator teres syndrome). The radial nerve may be compressed in the axillary region by the improper use of a crutch, or in the arm when pressure is applied by a tourniquet, a hard surface, or the body's weight. Radial nerve compression in the arm is especially likely to occur when consciousness is reduced by anesthesia, sedatives, or alcohol intoxication. Handcuffs or other tight-fitting objects at the wrist—for example, watchbands or bracelets—may injure the median, ulnar, or superficial radial sensory nerves. The history should include review of occupation, hobbies, and recent changes in physical activity. Sporting activities, playing musical instruments, gardening, and knitting are examples of physical activities that could predispose to compressive nerve injuries.
   b. **Trauma** often causes UE pain and sensorimotor complaints. Even remote trauma may contribute to UE pain or sensorimotor symptoms. Examples include entrapment of a nerve by the callus of a healing fracture and development of a central cavity in the spinal cord (syringomyelia).
      (1) **Motor vehicle accident (MVA).** The severe trauma of a MVA may cause multiple neurologic complications including vertebral fracture with direct spinal cord injury, nerve-root avulsion, radiculopathy, brachial plexus injury, peripheral nerve injury, or late development of syringomyelia. Arm traction or stretching the arm and neck in opposite directions may cause cervical root avulsions or a stretch injury to the brachial plexus. An MVA may cause more than one PNS disorder—for example, cervical nerve-root avulsions and concomitant peripheral nerve injury. After an MVA, attention to multiple life-threatening injuries, or casting for multiple limb fractures, may preclude detection of PNS disorders until late in the course of recovery.
      (2) **Fractures and dislocations** may cause specific nerve injuries. Shoulder dislocation or fracture of the humerus may injure the axillary nerve. Fracture of the clavicle may injure components of the brachial plexus. Fracture of the humerus predisposes to radial nerve injury in the spiral groove, whereas fracture or dislocation of the radius may injure the posterior interosseous nerve (PIN) branch of the radial nerve. Fracture of the elbow predisposes to ulnar mononeuropathy, which may not manifest until years after the trauma, hence the name "tardy ulnar palsy." A wrist fracture may cause either median or ulnar mononeuropathy.
      (3) **Laceration.** When UE pain or sensorimotor symptoms begin after a skin laceration or puncture wound, direct injury to a nerve needs to be considered. Exploration is needed to determine if the nerve requires repair.
   c. **Physiologic compression sites.** The median and ulnar nerves are vulnerable to injury at specific sites where normal ligamentous and bony structures predispose to physical compression. The common compression sites are the wrist for the median nerve (carpal tunnel) and the elbow for the ulnar nerve (cubital tunnel). At these locations, the nerves are particularly susceptible to compression injury, hence the term "physiologic compression sites." A patient with UE sensorimotor symptoms, without any clear predisposing factors, is likely to have an abnormality of one of these nerves.
   d. **Systemic illnesses.** Systemic illness may predispose to the development of PNS disorders that manifest as UE sensorimotor symptoms. A complete listing of systemic

illnesses with PNS complications exceeds the scope of this chapter, but several common examples are given.

(1) **Endocrine disorders.** Patients with diabetic polyneuropathy are more vulnerable to development of mononeuropathies at physiologic compression sites. Patients with hypothyroidism are prone to developing CTS.

(2) **Rheumatologic disorders.** Several rheumatologic disorders predispose to UE nerve or nerve-root injury. Rheumatoid arthritis causes joint and degenerative bone disease that may lead to cervical radiculopathy, CTS, and PIN injury. Systemic vasculitis may involve individual peripheral nerves in either the upper or lower extremities. Abrupt onset of a mononeuropathy is occasionally the presenting manifestation of systemic vasculitis. Primary and hereditary amyloidosis are associated with CTS.

(3) **Renal failure and dialysis.** Patients receiving chronic hemodialysis are particularly likely to develop CTS, owing to the deposition of amyloid material (β-2 microglobulin) within the carpal tunnel. Placement of arteriovenous fistulas for hemodialysis may cause median or ulnar neuropathies and, less often, a severe distal ischemic injury to all UE nerves, called ischemic monomelic neuropathy. Diabetic patients seem particularly prone to this severe nerve injury.

(4) **Malignancy.** A patient with a history of cancer—particularly of the breast or lung—who develops UE sensorimotor complaints needs to be evaluated for metastases to the brachial plexus. Patients with radiation therapy to the brachial plexus region can develop radiation-induced brachial plexopathy, which may begin many years after radiation therapy.

3. **Other history.** The medical history should also include inquiry about symptoms of depression and a review of the social situation for factors that might influence the patient's symptoms. Specific questions should be asked regarding employment, accidents, work injuries, and possible litigation. Evidence of CNS disease should be sought, which might include seizures, disturbed consciousness, personality change, or problems with cognition, language, or vision.

B. Physical examination.

1. **Motor examination.**

a. **Muscle inspection.** Muscles are inspected for atrophy and spontaneous muscle contractions. Muscle atrophy is present when reduction of the normal muscle bulk is revealed by visual inspection or direct measurement of limb circumference. Atrophy of specific muscles helps localize the disorder. Atrophy of the thenar eminence alone suggests a disorder of the median nerve or the deep terminal branch of the ulnar nerve. Atrophy of the thenar and hypothenar areas and the interossei muscles should raise considerations of combined median and ulnar mononeuropathies, lower trunk brachial plexopathy, C8–T1 radiculopathy, or C8–T1 spinal cord disease. Winging or elevation of one scapula suggests a long thoracic nerve mononeuropathy. Muscle inspection also involves a careful search for fasciculations, which are fine muscle twitches visible through the skin. Fasciculations may occur infrequently as an isolated finding in asymptomatic individuals. However, when present in conjunction with muscle weakness and atrophy, fasciculations are a sign of a lower-motor neuron process. The exam should include inspection for fasciculations in all four limbs, as well as in the back and abdomen. Fasciculations occur most commonly with anterior horn cell diseases—for example, amyotrophic lateral sclerosis—but can also occur with diseases affecting the motor root, plexus, or peripheral nerve.

b. **Muscle strength ratings.** Muscle strength is assessed with manual muscle testing using the Medical Research Council strength rating scale (Table 22.1). It should be tested in proximal and distal muscles in all four limbs. This allows quantification of weakness and may reveal weakness the patient was not aware of. Muscles that should be tested bilaterally in the UE include muscles for arm abduction (deltoid and supraspinatus), arm external rotation (infraspinatus), elbow flexion (biceps), elbow extension (triceps), wrist flexion (flexor carpi radialis and flexor carpi ulnaris), wrist extension (extensor carpi radialis), finger flexion (flexor digitorum [FD] superficialis

and FD profundis), finger extension (extensor digitorum communis), finger spreading (interossei), thumb abduction (abductor pollicis brevis), and grip strength.

Patients with MSK disorders and patients with depression, psychological disturbances, or malingering may exhibit a type of weakness known as "breakaway" weakness, in which incomplete effort gives the appearance of weakness. Features suggesting breakaway weakness include pain complaints during testing, reasonable initial strength that decreases, variability in motor performance on serial exams, improved strength with encouragement, and absence of other objective signs of motor impairment. Patients with breakaway weakness due to a psychological disturbance or malingering often make facial expressions or body contortions to convey that great effort is being made.

c. **Muscle tone** is assessed by noting how easily the patient's limbs can be passively moved while the patient is asked to relax the limb tested. The tone is rated according to the Ashworth scale, in which normal tone is assigned a value of 1, and values 2 to 5 represent increasing degrees of abnormal stiffness. Muscle tone should be normal with all of the common PNS disorders causing UE pain and sensorimotor symptoms. Increased muscle tone raises the question of a CNS disorder. When increased muscle tone occurs with UE weakness and atrophy, a compressive lesion of the cervical spine or amyotrophic lateral sclerosis should be considered.

2. **Reflexes** are tested bilaterally in all four limbs, including the brachioradialis (C5–C6), biceps (C5–C6), triceps (C7–C8), quadriceps (L2–L4), and soleus (S1) tendons. They are rated as normal, decreased, or increased. A significant reflex asymmetry suggests an abnormality of the nervous system. Radiculopathy involving a cervical root typically depresses the corresponding UE reflex on the affected side. Brachial plexopathy causes decreased reflexes corresponding to the part of the plexus involved. Patients with C8–T1 radiculopathy or lower-trunk brachial plexopathy may exhibit normal UE reflexes. Mononeuropathies of the UE do not usually influence the UE reflexes, unless the nerve involved supplies the muscle tested in the reflex arc—for example, musculocutaneous nerve mononeuropathy may cause a reduced biceps reflex. Reflexes are preserved in MSK disorders and increased in CNS disorders.
3. **Sensory examination.** The sensory examination involves testing of light touch, pain (pinprick), vibration, and joint position sensations in the upper and lower extremities. Particular attention is paid to cutaneous areas where there are sensory complaints.
4. **Maneuvers.** Several maneuvers may aid in the evaluation of UE sensorimotor complaints. Tinel's sign, originally described for the assessment of regenerating nerve fibers, is now commonly employed to elicit paresthesias radiating in a nerve's cutaneous distribution. It is elicited by gentle tapping over a nerve. It may be observed in association with regenerating nerve fibers, neuroma, focal demyelination, and even in normal individuals. Tinel's sign is easier to elicit from a diseased nerve than from a normal nerve, and thus it may help to localize an abnormal nerve. It is commonly used to assess for CTS by tapping over the median nerve on the volar surface of the wrist. With Phalen's maneuver, the wrist is flexed for up to 1 minute to elicit paresthesias in the median nerve distribution. A positive Phalen's maneuver provides supportive evidence for CTS. Adson's maneuver refers to assessing the radial pulse when the arm is abducted and extended. Loss of the radial pulse with this maneuver is alleged to indicate compression of the subclavian artery by a cervical rib or a hypertrophied scalenus muscle. However, it is not a useful test because it is subjective and may cause normal individuals to lose their radial pulse.

C. Laboratory studies.

1. The EDS consist of nerve conduction velocity (NCV) studies and EMG. These tests permit an objective and quantitative assessment of individual peripheral nerves and muscles. They can substantiate a clinically suspected diagnosis or reveal unsuspected abnormalities. With rare exceptions, all patients with symptoms of UE pain and sensorimotor symptoms should have EDS as part of the initial diagnostic evaluation. When performed in the first few days after the onset of nerve injury, EDS do not reveal as many abnormalities as when performed 7 to 10 days later. However, performing EDS early after injury allows the opportunity to document preexisting abnormalities. This may be important for complicated diagnostic cases or when medicolegal issues occur. Detailed discussion of EDS is found in Chapter 33.

2. **Radiologic studies.**
   a. **Plain films.** After head or neck trauma, cervical spine films are necessary to evaluate for fractures. When cervical radiculopathy is suspected, cervical spine films may reveal narrowing of specific neural foramina. Cervical spine films may also be useful in detecting a cervical rib, which should be investigated when clinical and EDS evidence suggests a neurogenic thoracic outlet syndrome (TOS). The patient with brachial plexopathy should have a chest film to evaluate for malignancy. If clinical evidence suggests Pancoast's syndrome, apical chest film views should be included to search for an apical tumor. Plain films may also be useful in the evaluation of MSK disorders, by revealing evidence of degenerative arthritis or tendon calcifications.
   b. **MRI.** Cervical spine MRI studies are usually performed to evaluate cervical radiculopathy. Myelography combined with CT may be used when MRI is not an option. MRI of the brachial plexus is often used to search for evidence of tumor as the cause of brachial plexopathy.
   c. **Laboratory studies** for the investigation of systemic illnesses are obtained for patients with UE sensorimotor complaints, depending on individual case circumstances. Tests that may be useful include CBC with differential, chemistry panel, blood sugar, erythrocyte sedimentation rate, antinuclear antibody, urinalysis, serum immunofixation electrophoresis, thyroid function, and occasionally, spinal fluid tests.

D. **Unexplained symptoms.** When thorough evaluation of UE pain or sensorimotor symptoms does not reveal a specific PNS or MSK disorder, alternative explanations must be considered. Possibilities include positional nerve compression, CNS disease, depression, psychological factors, or malingering. The symptoms and signs of CNS and PNS diseases may overlap, particularly for slowly progressive conditions—for example, brain tumor or multiple sclerosis. Clues suggesting CNS disease include painless weakness or sensory disturbance, upper-motor neuron signs, altered consciousness or personality, or problems with cognition, language, or vision. Depression may present with unexplained UE pain or sensorimotor symptoms. Some patients may not have frank depression but unhappiness or conflict in the psychosocial realm, which manifests as neurologic symptoms. Such patients often deny a relationship between their psychological state and neurologic symptoms. Others have onset of symptoms after accidents or injuries, and either the process of litigation or the power of suggestion from inquisitive physicians distorts the usual concept of wellness and perpetuates the symptoms. Patients with unexplained symptoms should have neurologic consultation and may need to be followed and observed over time.

III. DIAGNOSTIC APPROACH

The history provides initial hypotheses about the cause of the symptoms, and these hypotheses are tested during the physical examination. Knowledge of PNS anatomy is essential for interpreting UE sensorimotor symptoms and signs. In almost all cases, EDS are performed to help localize or exclude a suspected PNS disorder. When a PNS disorder is present, EDS help determine the severity and type of pathologic process. Additional diagnostic assessments may include radiologic studies or laboratory tests, depending on individual patient circumstances.

IV. SELECTED DISORDERS AND CRITERIA FOR DIAGNOSIS

A. **Peripheral nervous system disorders.**
1. **Mononeuropathy.**
   a. **Median nerve.**
      (1) **CTS.**
         (a) **Anatomy and etiology.** CTS is a very common disorder caused by compression of the median nerve at the wrist within the unyielding space known

as the carpal tunnel. Many disorders compromise this space, resulting in median nerve compression. The most common cause is flexor tenosynovitis, which may be associated with excessive physical use of the hands. Patients with primary carpal stenosis—that is, a narrow carpal tunnel—may be especially prone to CTS. Other local factors causing CTS include vascular lesions, abnormal tendons, ganglion cysts, tumoral calcinosis, pseudoarthrosis, and infection. Systemic disorders associated with CTS include endocrine disorders such as hyperparathyroidism, acromegaly, and hypothyroidism, and rheumatologic disorders such as rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, temporal arteritis, scleroderma, and gout. Other conditions predisposing to CTS include diabetic and other polyneuropathies, chronic hemodialysis, shunts for hemodialysis, and pregnancy.

(b) **Clinical features of CTS** include numbness or tingling involving one or more of the first four digits (thumb through ring finger), although occasionally the entire hand is involved. There may be pain in the fingers or wrist, and occasionally in the forearm or shoulder. Patients are often awakened at night by these symptoms, and physical activity with the hands may exacerbate symptoms. Advanced cases can develop weakness and atrophy of the thenar muscle. Physical examination reveals decreased sensation in the volar aspect of the first four digits. Because the median nerve innervation frequently supplies only the lateral half of the ring finger, sparing of sensation on the medial half of the ring finger is a helpful sign. Advanced cases show weakness and atrophy of the abductor pollicis brevis. Tinel's and Phalen's signs may be present.

(c) **Diagnosis** of CTS is established by clinical history, physical findings, and EDS. The EDS findings vary with the severity of the disorder. In mild cases, the amplitude of the median compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) are normal, and the wrist latency values are prolonged. The median NCV reveals focal slowing across the wrist. Slowing of NCV in proximal median nerve segments should not exclude the diagnosis of CTS. In some cases, there may be conduction block at the wrist level. In more advanced cases, the median CMAP and SNAP amplitude values are reduced, and fibrillation potentials may occur in the abductor pollicis brevis muscle. The ulnar nerve studies in the same hand are normal.

(2) **Pronator teres syndrome.**

(a) **Anatomy and etiology.** The pronator teres syndrome refers to compression of the median nerve in the forearm where it passes between the heads of the pronator teres muscle. This uncommon disorder is usually related to an occupation involving repetitive pronation of the forearm, which leads to hypertrophy of the pronator teres muscle. Other causes include a fibrous band from pronator teres to FD superficialis, or local trauma.

(b) **Clinical features.** The predominant symptom is pain in the volar forearm. Median innervated muscles, including the pronator teres, remain strong. Median sensory function is typically normal. Examination may show tenderness in the region of the pronator teres muscle, and there may be a Tinel's sign over the pronator muscle.

(c) **Diagnosis** is established primarily by clinical features. EDS are often normal, but occasionally, slow median NCV may be observed in the forearm segment.

(3) **Anterior interosseous syndrome.**

(a) **Anatomy and etiology.** This relatively uncommon median nerve disorder involves compression of the anterior interosseous branch of the median nerve in the forearm, usually by a fibrous band from the pronator teres or the FD superficialis muscles. Other forearm anomalies or forearm trauma may also cause the disorder. The anterior interosseous nerve (AIN) is a purely motor nerve that supplies the flexor pollicis longus (FPL), FD I and II, and pronator quadratus muscles.

(b) **Clinical features** include forearm or elbow pain combined with weakness of flexion of the distal phalanx of the thumb (FPL) and the index and middle fingers (FD). Patients note inability to pinch the thumb and index finger together. Pronation strength is preserved as the pronator teres muscle is unaffected.

(c) **Diagnosis** is established by the above-mentioned clinical features and EDS. The median NCV studies are normal. The EMG shows fibrillation potentials confined to one or more of the above muscles supplied by the AIN. When AIN causes weakness confined to the FPL, EMG is extremely helpful for differentiating a partial AIN syndrome from rupture of the FPL tendon.

b. **Ulnar nerve.**

(1) **Cubital tunnel syndrome.**

(a) **Anatomy and etiology.** The ulnar nerve may become compressed in the elbow region either in the condylar groove or the cubital tunnel. The cubital tunnel is formed on the sides by the two heads of the flexor carpi ulnaris muscle with a floor (medial ligament of the elbow) and roof (aponeurosis of the flexor carpi ulnaris muscle) completing the boundaries. The ulnar nerve runs through this space and then underneath the flexor carpi ulnaris muscle. Remote elbow trauma, with or without fracture, predisposes to later development of entrapment neuropathy in the elbow region (tardy ulnar palsy). However, many patients develop ulnar neuropathy without antecedent trauma. Repetitive movement at the elbow or prolonged flexion of the elbow may be predisposing factors.

(b) **Clinical features** include sensory complaints in the ulnar division of the hand (the fifth digit and the medial half of the fourth) and the ulnar-innervated portion of the hand and wrist. Sensory complaints may include decreased sensation, paresthesias, and pain. Pain may involve the medial forearm and elbow. Weakness involves the interossei, abductor digiti minimi, adductor pollicis, and flexor pollicis brevis. When weakness is chronic, atrophy may occur, and a claw hand deformity may develop. Most often, the flexor carpi ulnaris muscle remains strong. A diagnosis of ulnar neuropathy requires normal strength in C8–T1 muscles innervated by the median and radial nerves.

(c) **Diagnosis** is established by the characteristic history, physical findings, and EDS. Ulnar neuropathy at the elbow may show reduction of the ulnar CMAP and SNAP. There may be evidence of conduction block in motor fibers that can be localized to the elbow region. Ulnar NCV may be focally slow across the elbow. The EMG may show fibrillation potentials and/or abnormal motor unit potentials (MUPs) in ulnar-innervated hand muscles. Usually, the flexor carpi ulnaris does not show fibrillation potentials, although it may if its motor branch is also compressed.

(2) **Compression at the wrist (Guyon's canal).**

(a) **Anatomy and etiology.** Guyon's canal is a fibro-osseous tunnel connecting the pisiform and hamate wrist bones through which the ulnar nerve travels. As the ulnar nerve emerges from Guyon's canal, it divides into motor and sensory branches. The deep terminal branch is purely motor and supplies all of the ulnar-innervated hand muscles. The superficial terminal branch supplies sensation to the medial distal half of the palm and the palmar surfaces of the fourth and fifth digits. Sensation to the medial proximal half of the palm is supplied by the palmar cutaneous branch of the ulnar nerve, which arises in the mid-forearm and does not pass through Guyon's canal. Sensation to the medial dorsal half of the hand is supplied by the dorsal cutaneous branch of the ulnar nerve, which arises above the wrist and does not pass through Guyon's canal. Factors predisposing to ulnar neuropathy at the wrist include chronic compression, which may occur in cyclists and local trauma—for example, wrist fracture.

(b) **Clinical features** vary depending on the precise level of abnormality. Compression of the entire ulnar nerve within Guyon's canal or of the two

branches as they leave the canal causes weakness of all ulnar-innervated hand muscles and sensory loss in the superficial terminal branch distribution. Sensation of the dorsal medial hand and the proximal half of the medial palm is spared because sensation is supplied by other branches. Compression of the deep terminal motor branch may occur in isolation either before or after it supplies the hypothenar muscles, producing ulnar-innervated hand muscle weakness with no sensory loss. Finally, compression of only the superficial terminal branch causes sensory loss in its palmar distribution with normal hand strength.

(c) **Diagnosis** is established by clinical examination and EDS. The EDS findings vary depending on which of the above-mentioned ulnar nerve branches is involved. If the superficial terminal sensory branch is involved, NCV studies will show a reduced or absent ulnar SNAP recorded from the fifth digit, but the SNAP from the dorsal ulnar cutaneous nerve remains normal. If the abnormality involves the deep terminal branch, ulnar CMAP amplitude may be reduced and there may be fibrillation potentials or abnormal MUPs in ulnar-innervated hand muscles.

c. **Radial nerve.**

(1) **Axilla or spiral groove compression.**

(a) **Anatomy and etiology.** The radial nerve may be compressed against the humerus by external pressure in the axilla or the spiral groove. Compression in the axilla can be caused by improper use of crutches. Compression in the spiral groove is likely to occur when an individual falls asleep with the arm hanging over a chair or with a partner's head against the arm. Radial nerve compression is especially likely if use of alcohol or sedatives prevents the patient from normal turning during sleep. The term "Saturday night palsy" has been used for such a radial nerve palsy. A similar outcome may follow use of an arm tourniquet during surgery. The radial nerve may also be injured in the spiral groove by blunt trauma, fractures of the humerus, and rarely by vigorous arm exercise.

(b) **Clinical features** are weakness of radial-innervated muscles and sensory loss on the dorsal aspects of the hand, thumb, and index and middle fingers. Radial-innervated muscles include triceps, brachioradialis, supinator, and the wrist and finger extensors. The triceps is affected by radial nerve compression in the axilla but spared with spiral groove compression. Weakness of wrist extensors causes wrist drop. Inability to stabilize the wrist prevents normal hand interossei muscle function giving the false impression that ulnar-innervated hand muscles are weak.

(c) **Diagnosis** of radial mononeuropathy is confirmed by clinical features and EDS. Nerve conduction studies show a reduced-amplitude radial CMAP and reduced or absent SNAP. The presence or absence of fibrillation potentials in triceps helps to localize the compression site (axilla or spiral groove).

(2) **PIN.**

(a) **Anatomy and etiology.** The PIN is the purely motor termination of the radial nerve in the forearm. The PIN supplies the supinator muscle and the wrist and finger extensors. Entrapment of the PIN is relatively uncommon. When this occurs, it is usually at the level of the supinator muscle. Predisposing factors include vigorous use of the arm, fracture of the head of the radius, and other local traumas. Hypertrophied synovia of the elbow joint in patients with rheumatoid arthritis may compress the PIN.

(b) **Clinical features** are weakness of the wrist and finger extensors. Some patients have pain in the elbow or dorsal forearm. There are no sensory abnormalities apart from pain because the PIN is purely motor.

(c) **Diagnosis** is established by the above-mentioned clinical features and EDS. NCV studies show a reduced-amplitude radial CMAP and normal radial SNAP. The EMG exam shows fibrillation potentials and abnormal MUPs in the aforementioned radial-innervated muscles.

(3) **The superficial sensory branch.**
   (a) **Anatomy and etiology.** The superficial sensory branch of the radial nerve arises in the vicinity of the elbow and supplies sensation to the dorsolateral hand and the dorsal aspects of the first three digits. It may be injured at the wrist level by local trauma or compression from tight objects around the wrist such as watchbands or handcuffs.
   (b) **Clinical features** are purely sensory, with paresthesias and sensory loss in the radial sensory distribution.
   (c) **Diagnosis** is made by the history, physical findings, and NCV evidence of a reduced or absent superficial radial SNAP.

d. **Axillary nerve.**
   (1) **Anatomy and etiology.** The posterior cord of the brachial plexus divides into the radial and axillary nerves. The axillary nerve travels below the shoulder joint and supplies the teres minor muscle, which externally rotates the arm. The axillary nerve then courses behind and lateral to the humerus before dividing into anterior and posterior branches, which supply corresponding portions of the deltoid muscle. The posterior branch gives a cutaneous nerve that supplies the skin over the lateral deltoid. The axillary nerve may be injured by shoulder dislocation or fractures of the humerus. It may be the only nerve affected by idiopathic brachial plexopathy (see below).
   (2) **Clinical features.** The main clinical manifestation is impaired shoulder abduction resulting from deltoid weakness. The supraspinatus initiates arm abduction, so patients may retain limited arm abduction. Weakness of the teres minor muscle may be difficult to demonstrate on physical examination because of normal infraspinatus muscle function. Sensory loss may be demonstrated over the lateral portion of the deltoid muscle.
   (3) **Diagnosis** is confirmed by weakness limited to the deltoid muscle and EMG abnormalities restricted to the deltoid and teres minor muscles. An axillary NCV study with surface recording from the deltoid muscle may show delay or reduced amplitude of the axillary nerve CMAP.

e. **Musculocutaneous nerve.**
   (1) **Anatomy and etiology.** The musculocutaneous nerve arises from the lateral cord of the brachial plexus and supplies the coracobrachialis, biceps, and brachialis muscles. It continues in the forearm as the purely sensory lateral antebrachial cutaneous nerve. Mononeuropathy of the musculocutaneous nerve is uncommon, but it may occur with shoulder dislocation, direct trauma or compression, or sudden extension of the forearm.
   (2) **Clinical features** include impaired arm flexion resulting from weakness of the biceps and the other musculocutaneous-innervated muscles. The biceps reflex may be normal or reduced, depending on the severity of the biceps weakness. Sensory loss is present over the lateral forearm.
   (3) **Diagnosis.** The clinical features of musculocutaneous neuropathy closely parallel those of C5 radiculopathy. Diagnosis is established by the above-mentioned clinical features and EDS results that differentiate C5 radiculopathy from musculocutaneous nerve mononeuropathy. The lateral antebrachial SNAP is reduced or absent in musculocutaneous neuropathy but normal in C5 radiculopathy. EMG shows involvement of only muscles supplied by the musculocutaneous nerve.

f. **Long thoracic nerve.**
   (1) **Anatomy and etiology.** The long thoracic nerve is a purely motor nerve arising from the ventral rami of the C5, C6, and C7 spinal nerves. It courses along with other brachial plexus components underneath the clavicle, and then travels down the chest wall anterolaterally to supply the serratus anterior muscle. This large muscle fixes the scapula to the chest wall, providing general stability for the shoulder during arm movements. Injury of the long thoracic nerve may occur with trauma or with vigorous physical activities involving shoulder girdle movements. Long thoracic neuropathy may be caused by idiopathic brachial plexopathy.

(2) **Clinical features** of long thoracic mononeuropathy include pain and weakness in the shoulder. Patients have difficulty abducting the arm or raising it above the head. Winging of the scapula is demonstrated by having the patient extend the arms forward and push against a wall. The scapula elevates from the chest wall because the weak serratus muscle cannot hold it.

(3) **Diagnosis** is established by the above-mentioned clinical features and EMG showing fibrillation potentials involving only the serratus anterior muscle. Long thoracic nerve NCS are technically difficult and other NCS are normal.

g. **Suprascapular nerve.**

(1) **Anatomy and etiology.** The suprascapular nerve is a purely motor nerve arising from the upper trunk of the brachial plexus and passing through the suprascapular notch on the upper border of the scapula to supply the supraspinatus and infraspinatus muscles. The suprascapular nerve is most often injured by trauma in which there is excessive forward flexion of the shoulder. It may be involved in idiopathic brachial plexopathy.

(2) **Clinical features** are pain in the posterior shoulder and weakness of the spinati muscles. The supraspinatus initiates arm abduction, whereas the infraspinatus externally rotates the arm.

(3) **Diagnosis** is established by clinical history, physical findings, and EDS. Routine NCV studies are normal, but motor NCV studies with recording from the supraspinatus muscle may show reduced amplitude or prolonged latency relative to the unaffected side. The EMG exam shows abnormalities confined to the spinati muscles on the affected side.

h. DSN.

(1) **Anatomy and etiology.** The DSN is a purely motor nerve arising from the upper trunk of the brachial plexus and passing through the scalenus medius muscle to supply the rhomboid and levator scapulae muscles. Injury to the DSN is uncommon.

(2) **Clinical features** include pain in the scapular region and weakness of the rhomboid and levator scapulae muscles.

(3) **Diagnosis** is established by clinical features and EMG showing fibrillation potentials restricted to the muscles supplied by the DSN. There is no satisfactory NCS for the DSN.

2. Brachial plexopathy.

a. **Idiopathic brachial plexopathy.**

(1) **Anatomy and etiology.** Idiopathic brachial plexopathy, also known as Parsonage–Turner's syndrome or neuralgic amyotrophy, is an uncommon condition believed to represent an immune-mediated neuropathy affecting various portions of the brachial plexus. An antecedent event, such as an upper respiratory infection or immunization, is present in about half of the cases.

(2) **Clinical features.** The main clinical features are abrupt onset of severe pain in the shoulder and proximal arm followed at a variable interval (hours to weeks) by shoulder and arm muscle weakness. The pain is exacerbated by the movement of the arm, shoulder, or neck, which may give the false impression of an MSK disorder. Any combination of muscles innervated by nerves arising from the brachial plexus may be involved, but there is a predilection for proximal muscles. Muscles supplied by the axillary, suprascapular, long thoracic, radial, musculocutaneous, and AINs are commonly involved. The nerve involvement may be extensive or restricted to a single nerve. Asymmetric contralateral involvement occurs in one-third of patients. Sensory loss or paresthesias may be present, but these features are relatively minor.

(3) **Diagnosis** is established by the characteristic clinical history, physical findings, and EDS. Patients with this disorder typically present early for evaluation and treatment for the severe pain. If EDS are performed early, abnormalities of MUP recruitment may be observed, but the studies may be otherwise normal. If EDS are repeated 7 to 10 days after weakness begins, the NCS show evidence of axonal injury, with the distribution varying according to the specific nerves involved. An EMG shows fibrillation potentials in clinically weak muscles, and

often in muscles that were not judged weak by physical examination. For this reason, EMG is essential for determining the extent of injury.

b. Neurogenic TOS.
   (1) **Anatomy and etiology.** The "true" neurogenic TOS is a very rare disorder in which the lower trunk of the brachial plexus is compressed by an elongated transverse process of C7, a rudimentary cervical rib, or a fibrous band running from either of these to the first rib.
   (2) **Clinical features** are weakness and wasting of the intrinsic hand muscles, most markedly affecting the abductor pollicis brevis muscle; pain involving the medial forearm or hand; and sensory loss involving the fourth and fifth fingers and the medial hand and distal forearm.
   (3) **Diagnosis** is established by clinical features and characteristic EDS results. Radiographic evidence of an elongated C7 transverse process or a rudimentary cervical rib is helpful but not mandatory for diagnosis, because the structural problem may be a fibrous band that cannot be detected on imaging studies. The nerve conduction findings include severely reduced or absent median CMAP, normal median SNAP, reduced or absent ulnar SNAP, and mildly reduced or normal ulnar CMAP. The EMG exam shows fibrillation potentials in lower-trunk-innervated muscles, particularly those supplied by the median and ulnar nerves. In contrast to the rare and well-defined true neurogenic TOS is a condition commonly misdiagnosed as TOS, which has various UE sensorimotor symptoms but no consistent clinical history. Patients said to have this form of TOS have no objective neurologic abnormalities and no abnormalities on EDS. This form of TOS has been aptly referred to as "disputed" neurogenic TOS, and its existence as an entity remains controversial. Patients erroneously diagnosed with this type of TOS are often subjected to first-rib resection, and, unfortunately, severe brachial plexopathy may be a complication.

c. **Brachial plexopathy in patients with malignancy.**
   (1) **Anatomy and etiology.** Metastasis to the brachial plexus needs to be considered whenever a patient with a history of malignancy (especially breast or lung cancer) develops UE pain or sensorimotor symptoms. Brachial plexopathy is usually not the presenting feature of malignancy, except in Pancoast's syndrome, in which an apical lung carcinoma invades the lower trunk of the brachial plexus. For patients who have undergone prior chest wall radiotherapy, brachial plexopathy from radiation injury may occur as a later complication.
   (2) **Clinical features** of brachial plexopathy resulting from tumor invasion are pain, weakness, and sensory changes that more commonly affect the lower plexus. Unlike idiopathic brachial plexopathy, malignant brachial plexopathy has a gradual onset of symptoms, and lymphedema of the arm is common. In Pancoast's syndrome, patients usually first have pain in the medial arm and may develop sensorimotor abnormalities in the lower-trunk distribution. Horner syndrome (ipsilateral ptosis, miosis, and facial anhidrosis) often results from a tumor invading the inferior cervical sympathetic ganglion. Malignant plexopathy is more likely than radiation plexopathy to be painful and involve the lower trunk.
   (3) **Diagnosis.** A patient with a history of malignancy and new onset UE sensorimotor symptoms or pain should have EDS to exclude common conditions such as mononeuropathy or radiculopathy, which might cause symptoms identical to those of brachial plexopathy. The EDS can determine if there is evidence of brachial plexopathy and clarify the locations of abnormalities within the plexus. This information can help in planning and interpreting MRI studies of the plexus, which should be performed to look for evidence of tumor. Patients with lower-trunk plexopathy should have apical chest film views to look for an apical lung tumor. Myokymic discharges detected by EDS in patients with prior chest wall radiotherapy support a diagnosis of radiation plexopathy but do not conclusively exclude tumor metastases.

3. **Cervical radiculopathy.** The clinical and electrodiagnostic features of cervical radiculopathy are mentioned above, and thoroughly reviewed in Chapter 22.

B. MSK disorders share in common the predominant symptoms of pain and an absence of other neurologic manifestations. In general, EDS are normal when MSK disorders are the cause of UE pain symptoms. However, it is common for an underlying neurologic disorder affecting the PNS to result in a secondary MSK disorder, in which case EDS may be abnormal as a result of the underlying neurologic disorder.

1. **Rotator cuff injury.** The rotator cuff comprises the tendons of the supra-spinatus, infraspinatus, teres minor, and subscapularis muscles, which fix the humeral head in the glenoid fossa during shoulder abduction and provide internal and external arm rotation. Rotator cuff inflammation (tendinitis) and tear are common causes of shoulder pain. Tendinitis results from repetitive minor trauma to the cuff, and tear may occur as a chronic stage of this degenerative process, or acutely from abrupt trauma. With tendinitis or tear, there is shoulder pain on arm abduction or on internal or external arm rotation. With tear, there may be weakness of rotator cuff functions, but EMG studies are negative. Plain films may reveal tendon or subacromial bursa calcifications. Ultrasound or an arthrogram of the shoulder may confirm a rotator cuff tear.
2. **Bicipital tendinitis.** Inflammation of the biceps tendon causes pain and tenderness in the anterior shoulder region. The pain may be reproduced by supination of the forearm against resistance or by flexion and extension of the shoulder. There are no neurologic abnormalities, and the diagnosis is established clinically.
3. **Adhesive capsulitis (frozen shoulder).** Loss of motion at the shoulder joint may result in adhesion of the joint capsule to the humerus. Shoulder pain from any cause can lead to immobility and subsequent adhesive capsulitis. Alternatively, weakness of shoulder girdle muscles from either PNS or CNS disorders may cause this problem. Whatever the cause, the joint becomes stiff, and attempted motion causes severe shoulder pain. Muscle atrophy may result from PNS disease, or secondarily from disuse. The diagnosis is usually made by the clinical features.
4. **Lateral epicondylitis (tennis elbow).** Overuse of the extensor carpi radialis muscles (wrist extensors), or direct trauma to their tendinous insertion on the lateral epicondyle, may lead to inflammation, degeneration, or tear of the tendons. This produces pain localized over the lateral epicondyle, which may be exacerbated by use of the forearm-wrist extensor muscles.

V. REFERRAL

Patients should be referred to a reliable EMG laboratory for EDS, as these studies facilitate accurate diagnosis. Establishing the diagnosis guides subsequent diagnostic testing and treatment decisions. In addition, EDS can estimate the severity of the abnormality, which can help to estimate prognosis. Neurologic consultation for UE pain or sensorimotor symptoms is appropriate at any stage of the evaluation process if there are questions concerning diagnosis or management.

Recommended Readings

Cailliet R, ed. *Neck and Arm Pain. Pain Series*. 2nd ed. Philadelphia, PA: Davis; 1981.

D'Arcy CA, McGee S. The rational clinical examination. Does this patient have carpal tunnel syndrome? *JAMA*. 2000;283(23):3110–3117.

Dawson DM. Entrapment neuropathies of the upper extremities. *N Engl J Med*. 1993;329:2013–2018.

Nakano KK. The entrapment neuropathies. *Muscle Nerve*. 1978;1:264–279.

Pecina MM, Krmpotic-Nemanic J, Markiewitz AD, eds. *Tunnel Syndromes*. Boca Raton, FL: CRC; 1991.

Stewart JD. *Focal Peripheral Neuropathies*. 4th ed. West Vancouver, B.C. Canada: JBJ Publishing; 2010.

CHAPTER

25 Approach to the Patient with Lower Extremity Pain, Paresthesias, and Entrapment Neuropathies

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Lower extremity pain and paresthesia are common symptoms of peripheral nervous system (PNS) disorders. Diagnosing a mononeuropathy requires that the motor, reflex, and sensory changes be confined to a single nerve and can, if necessary, be supported by electrodiagnostic studies (EDS).

Diagnosis and management of PNS disorders was once the sole domain of specialists. However, "reemergence" of generalists in health care has resulted in at least two major trends. The first, as expected, is that persons with such disorders are no longer under the sole care of a specialist. The second, somewhat "unintentional" effect, is that the role of specialists has become more demanding. Specialists need to develop a greater proficiency in differentiating neuropathy from radiculopathy, plexopathy, and other nonneurologic syndromes of pain, disturbed sensation, or weakness. This increasing competency occurs in the setting of fewer and more carefully selected laboratory investigations.

Fortunately, recognition of a neuropathy has always necessitated careful attention to the history and examination, skills that are expected of specialists, but "within reach" of a generalist. After localization, a ranking of potential etiologies is formulated, and further diagnostic evaluation is planned.

This chapter provides an outline of common as well as some infrequent forms of lower extremity neuropathy. Symptoms and findings are emphasized, and the most frequent etiologic considerations are mentioned. The importance of bedside examination is assumed throughout, but the application of diagnostic tests is also reviewed.

I. EVALUATION

A. History. Various aspects of the history help in narrowing the etiologies of a mononeuropathy. The nature of onset (abrupt or insidious), preceding events (injury, surgery, or illness), associated symptoms (fever, weight loss, or joint swelling), and aggravating or alleviating features (joint position or specific activities) are all important. Because the observed deficit can be similar regardless of etiology, historical information is instrumental in limiting the differential diagnosis.

B. Physical examination. Although motor and sensory symptoms and signs correspond to the distribution of a single peripheral nerve or branch, the degree of deficit and constellation of findings can vary. Motor signs may be clinically absent, or varying degrees of weakness, atrophy, or fasciculation may be found. Likewise, sensory symptoms can be positive (e.g., tingling, pricking, and burning), negative (hypesthesia), or, while corresponding to a sensory distribution of a nerve, may be most pronounced in its distal distribution. Therefore, the sensory examination should begin with the **patient's description** of the area of involvement. The **course of the nerve** should be evaluated and local areas of discomfort or the presence of a Tinel's sign (pain or paresthesia in the cutaneous distribution of a nerve elicited by light percussion over that nerve) sought. The relationship of sites of discomfort to adjacent anatomic structures helps in identifying sites of nerve entrapment or compression.

C. Diagnostic studies. Further evaluation may be necessary in confirming the presence and severity of a mononeuropathy and excluding more proximal sites of involvement (plexus or root) that can clinically mimic a mononeuropathy.

1. **EDS.** An EMG and nerve stimulation studies (NSS) are quite useful in the evaluation of mononeuropathies. They can aid in localization, detect bilateral but asymmetric nerve

involvement (or detect an underlying polyneuropathy), define severity, and provide prognostic information.

2. **Laboratory testing** is directed at identification of a systemic or generalized disease that may be a predisposing factor and with newer imaging techniques, at times, targeted fascicular nerve biopsy. Owing to the practical nature of this section, an exhaustive listing of the medical, systemic diseases or structural disorders that can cause a mononeuropathy is not provided. The Recommended Readings provide extensive tabulations of frequent as well as unusual etiologies.
3. **Imaging studies.** Radiographic imaging was previously undertaken to identify intrathoracic, abdominal, retroperitoneal, or pelvic masses that may lead to nerve root, plexus, or nerve injury, but now it is also applied to imaging the PNS directly. This role of imaging studies has considerably advanced now that MRI is the method of choice for delineating a focal site of involvement, characterizing and at times assisting in the diagnosis of a nerve lesion. However, its effectiveness not only depends on the necessary MRI hardware and software, but clinical expertise through an interdisciplinary and collaborative effort among physicians and clinical departments. Routine X-ray studies play a less significant role.

II. SPECIFIC FORMS OF MONONEUROPATHY

A. Femoral and saphenous neuropathy. Formed within the psoas muscle by fusion of the posterior divisions of the ventral rami of the L2–4 spinal nerves, the femoral nerve exits from the lateral border of the psoas and descends between it and the iliacus muscles (which it may also innervate), but under the fascia of the iliacus. Emerging under the inguinal ligament, lateral to the femoral artery, the nerve divides into motor branches, which supply the quadriceps muscles, and sensory branches to the anterior portion of the thigh (Figure 25.1). One major division, the saphenous nerve, descends medially within Hunter's (adductor) canal, accompanying the femoral artery. At the medial superior aspect of the knee, it emerges from the canal and, accompanying the saphenous vein, descends medially down the leg and ends at the medial aspect of the foot. The saphenous nerve supplies the sensory innervation to the medial aspect of the leg and foot.

1. **Etiology. Femoral neuropathy** is usually caused by trauma from surgery (intrapelvic, inguinal, or hip operations), stretch or traction injuries (prolonged lithotomy position in childbirth), or direct compression (hematoma within the iliacus compartment). Although diabetes mellitus is described as a frequent etiologic factor, such cases are misnomers and represent a restricted plexopathy or more diffuse lesions, but predominantly affecting femoral nerve function. **Saphenous neuropathy** is most often attributable to injury following surgery (peripheral vascular, saphenous vein removal, or knee operations).
2. **Clinical manifestations.**
   a. **History.** The patient reports leg weakness (as if the leg will "fold under") on attempting to stand or walk. Pain in the anterior part of the thigh accompanied by the abrupt onset of leg weakness is a frequent presentation of an iliacus (retroperitoneal) hematoma. A similar pattern of pain, but usually subacute in onset, can be observed in cases of "femoral neuropathy" occurring in diabetes mellitus. With the exception of pain, sensory involvement tends to be infrequent and a minimal symptom of femoral neuropathy.

      Because of its association with surgery, sensory loss in saphenous neuropathy may initially go unnoticed or be of little concern to the patient. However, pain may be prominent, and in such cases, it usually appears sometime after the assumed injury to the nerve.

   b. **Physical examination.**
      (1) **Neurologic.** Examination reveals weakness of the quadriceps muscles, absent or diminished patellar reflex, and sensory loss over the anterior thigh and, with saphenous nerve involvement, the medial aspect of the leg and foot.

(2) **General.** Examination or palpation within the inguinal region and, in cases of saphenous nerve involvement, the medial aspect of the knee may identify focal areas of pain and perhaps the site of involvement. The proximity of a surgical scar or point of injury can provide additional etiologic clues. In cases in which retroperitoneal hemorrhage is suspected, peripheral pulses may be normal, but there is characteristic posturing of the leg (held flexed at the hip), and attempts to extend or perform a reverse straight-leg test exacerbate the pain.

3. **Differential diagnosis.** Discovery of hip adduction weakness suggests a more proximal process, plexus or root as the site of involvement, although a superimposed obturator neuropathy cannot be excluded.

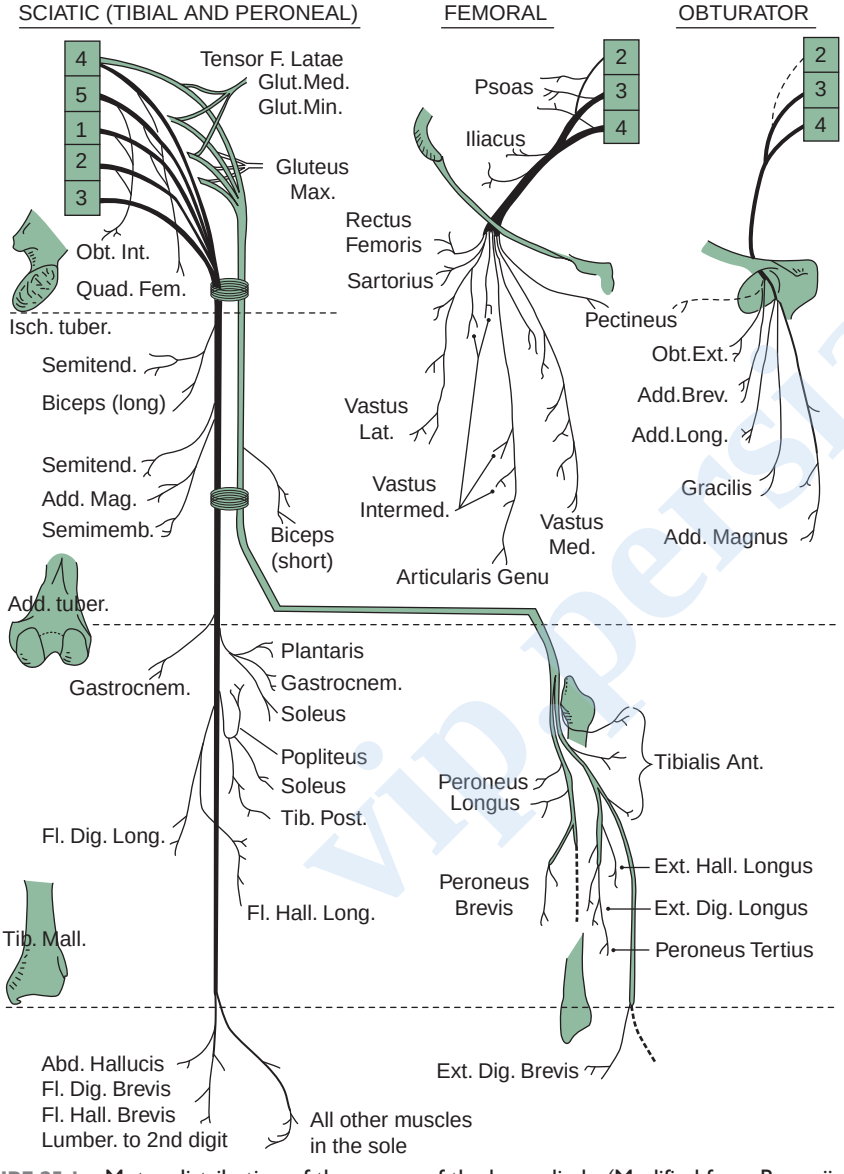

FIGURE 25.1 Motor distribution of the nerves of the lower limb. (Modified from Basmajian JV. *Grant's Method of Anatomy*. 9th ed. Baltimore, MD: Williams and Wilkins; 1975.)

4. **Evaluation.**
   a. **Electrodiagnostic.** NSS are not as helpful as EMG in the evaluation of a suspected femoral neuropathy. EMG includes study of other L2–4 innervated muscles and paraspinal muscles because they should not be involved in isolated femoral neuropathy.
   b. **Imaging.** CT or MRI of the retroperitoneum helps to identify cases resulting from retroperitoneal hemorrhage or suspected mass lesion.

B. Obturator neuropathy. Arising within the psoas muscle from ventral divisions of the L2–4 spinal nerves, the obturator nerve exits from the psoas muscle at its lateral margin, descends into the pelvis, and exits through the obturator foramen. It innervates the gracilis, adductor magnus, longus, and brevis muscles and supplies sensation to the upper medial aspect of the thigh.

1. **Etiology.** Isolated neuropathy of the obturator nerve is unusual. In cases resulting from pelvic or hip fracture, involvement of other nerves to the lower extremity or lumbosacral plexus also occur. Benign and malignant pelvic masses can result in obturator neuropathy, as can surgical procedures performed on those masses or within the pelvis.
2. **Clinical manifestations.**
   a. **History.** Leg weakness and difficulty walking are the most common first symptoms and usually overshadow sensory loss, if present.
   b. **Physical examination.**
      (1) **Neurologic.** Motor evaluation shows weakness of hip adduction, and sensory loss may be found along the upper medial thigh. The patellar reflex should be intact.
      (2) **General.** Careful pelvic and rectal examinations can identify an intrapelvic tumor and are necessary when obturator paralysis occurs without trauma.
3. **Differential diagnosis.** The presence of hip flexor or knee extensor weakness or an impaired patellar reflex suggests a lumbosacral plexopathy or L3–4 radiculopathy. In addition, sensory loss, which extends below the knee, is inconsistent with the expected sensory deficit.
4. **Evaluation.**
   a. **Electrodiagnostic.** NSS are not as helpful as EMG where involvement of other L2–4 muscles or paraspinal muscles identifies a more proximal lesion.
   b. **Imaging.** When obvious trauma is not a consideration, radiological imaging of the pelvic cavity is helpful when a mass or infiltrative lesion is suspected.

C. Lateral femoral cutaneous neuropathy. Dorsal divisions of the ventral primary rami of the L2–3 spinal nerves contribute to the lateral femoral cutaneous nerve, which emerges from the lateral border of the psoas major muscle. It then crosses laterally, within the fascia of the iliacus muscle, and crosses over the sartorius muscle before passing under the lateral border of the inguinal ligament. Piercing the fascia lata, it divides into anterior and posterior branches that provide sensory innervation to the anterolateral aspects of the thigh. Anatomic variation is frequent in regard to origin (it can arise as a branch of the femoral or genitofemoral nerve), course of its branches and extent of its sensory innervation.

1. **Etiology.** In most cases, entrapment or compression at or near the inguinal ligament is the assumed etiologic factor. However, entrapment or compression at other sites (i.e., retroperitoneal mass), surgical procedures (especially those involving retroperitoneal structures, pelvis, or inguinal sites), and trauma to the thigh can also injure the lateral femoral cutaneous nerve.
2. **Clinical manifestations.**
   a. **History.** Pain (burning or a "crawling" sensation) with variable loss of sensation on the anterolateral aspects of the thigh and exacerbated by walking or arising from a chair (**meralgia paresthetica**). Frequently, the patient rubs the thigh for relief.
   b. **Physical examination.**
      (1) **Neurologic.** The area of sensory change usually is small and over the lateral aspect of the thigh.
      (2) **General.** Careful palpation along the inguinal ligament and anterior pelvic brim will infrequently detect an area of tenderness or precipitate symptoms.
3. **Differential diagnosis.** The primary differential diagnosis is a femoral neuropathy. Lumbar plexopathy and L2 radiculopathy are considerations, but limited sensory impairment, lack of motor involvement, and intact reflexes help in excluding them.

4. **Evaluation.** Although clinical features usually provide enough support for a diagnosis, when uncertainty or a preexisting illness complicates the issue (retroperitoneal mass), further testing may be needed.

   Unlike the situation with other entrapment syndromes, responsiveness to treatment may help to "confirm" the diagnosis of lateral femoral cutaneous neuropathy. Subcutaneous injection of an anesthetic agent or steroid at the assumed exit point of the lateral femoral cutaneous nerve (medial to the anterior superior iliac spine and under the inguinal ligament) or at a site of local tenderness may relieve symptoms and support but does not confirm the diagnosis.

   a. **Electrodiagnostic.** Difficulty in eliciting a response from healthy or control subjects during NSS has limited the use of such testing. However, EMG studies play a more important role by clarifying unusual or unclear symptoms, because detection of clinically silent motor involvement implies involvement of more than the lateral femoral cutaneous nerve.
   b. **Imaging.** Radiographic imaging is not indicated. However, unexplained or concomitant gastrointestinal or urogenital symptoms should raise suspicion of a retroperitoneal or pelvic mass and then further evaluation is appropriate.

D. Sciatic neuropathy. The sciatic nerve arises from the ventral rami of the L4–5 spinal nerves, which, by way of the lumbosacral trunk, fuse with those from S1 to S3. Passing along the inner wall of the pelvis, it exits through the sciatic notch and passes under the piriformis muscle, where it lies between the ischial tuberosity and greater trochanter. Remaining in this deep location, the sciatic nerve descends into the extremity and proximal to the knee, divides into the peroneal and tibial nerves. The sciatic nerve itself is clearly divisible into two trunks—the medial, which receives contributions from the L4 to S3 rami and gives rise to the tibial nerve, and the lateral, the contributions of which are from L4 to S2 and from which the common peroneal nerve is derived. The sciatic nerve itself has no sensory branches. The lateral trunk provides innervation to the short head of the biceps femoris muscle and, by way of the medial trunk, the semitendinosus, semimembranosus, and long head of the biceps femoris muscles. With the obturator nerve, the adductor magnus muscle is also innervated.

1. **Etiology.** Most cases of sciatic neuropathy, whether involved at the gluteal level or the thigh, are secondary to trauma. (The sciatic nerve is possibly second to the peroneal nerve in this regard.) This includes injury to adjoining or neighboring structures in fracture of the pelvis, hip, or femur as well as from direct injury. Injection injuries are no longer as frequent, but compression injuries are increasing and often occur in the setting of prolonged immobility such as in various operative procedures (i.e., cardiac bypass graft surgery). Miscellaneous causes include entrapment by fibrous constricting bands, local hematoma, or tumor.

   Mention must be made of the **piriformis syndrome.** At this time, few cases rigorously support the assumed pathogenesis of this syndrome, compression of the sciatic nerve by the overlying piriformis muscle, although it remains a frequent clinical diagnosis. Point tenderness of the sciatic nerve at the level of the piriformis muscle can be found among patients with plexopathy or lumbosacral radiculopathy and does not necessarily confirm pathologic compression of the sciatic nerve by the piriformis muscle.

2. **Clinical manifestations.**
   a. **History.** Complete lesions are associated with paralysis of the hamstring muscles and all muscles below the knee. Sensory loss occurs in the tibial and peroneal distributions. Partial lesions, especially those of the lateral trunk, make up most cases of sciatic neuropathy and often manifest as foot-drop.
   b. **Physical examination.**
      (1) **Neurologic.** Although variable paralysis of muscles innervated by both the medial and lateral trunk can be present, involvement of muscles innervated by the lateral trunk is the most frequent presentation. Sensory loss is variable, but restricted to the distribution of the sensory branches of the peroneal and tibial nerves. The muscle stretch reflexes of the hamstring and Achilles' tendons can be depressed.
      (2) **General.** Palpation along the course of the nerve may help identify masses or locate points of pain and tenderness, but cannot entirely exclude more proximal nerve lesions.

3. **Differential diagnosis.** Care must be taken to ensure that a radiculopathy (especially L5–S1) is not masquerading as a sciatic neuropathy. The straight-leg-raise test, frequently positive in radiculopathy, can also be present in cases of lumbosacral plexopathy and sciatic neuropathy. A careful rectal and pelvic examination is indicated when sciatic neuropathy is suspected because involvement of the sacral plexus by a pelvic mass may not otherwise be identified. Finally, an isolated common peroneal or tibial neuropathy must be considered.
4. **Evaluation.**
   a. **Electrodiagnostic.** Both NSS and EMG are useful in differentiating sciatic mononeuropathy from L5 to S2 radiculopathies or plexopathy and require careful study of the paraspinal and gluteal muscles. Yet at times there can still be diagnostic confusion. When the lateral division of the sciatic nerve is "selectively" involved, EMG and NSS may show a pattern that suggests peroneal nerve involvement, whereas tibial nerve studies may appear to be normal.
   b. **Imaging.** In cases in which radiculopathy and plexopathy cannot be excluded, further radiological studies can provide useful information. In addition, in cases in which only sciatic nerve involvement is found, MRI with gadolinium infusion may effectively depict the course of the nerve and help in identifying focal abnormalities.

E. Peroneal neuropathy. Arising from posterior divisions of the L4–S2 ventral rami of spinal nerves, the common peroneal nerve descends into the leg as the lateral division of the sciatic nerve. At the level of the popliteal fossa, it branches from the sciatic nerve and moves toward the lower lateral portion of the popliteal fossa. Two cutaneous sensory branches arise at this point, one to the sural nerve and the other, the lateral (sural) cutaneous nerve of the calf, providing sensation to the upper lateral calf. Exiting laterally from the popliteal space, the peroneal nerve is in close juxtaposition to the fibula, winds below its head, and passes through a tendinous arch formed by the peroneus longus muscle. At its exit from the arch, the nerve divides into the superficial and deep peroneal nerves. The superficial peroneal nerve descends adjacent to the peroneus longus and brevis muscles, which it innervates, and in the distal third of the leg, it pierces the fascia. The terminal branches (medial and lateral) of the superficial peroneal nerve provide sensation to the lateral dorsal surface of the foot. The deep peroneal nerve enters the extensor compartment of the leg and with the tibial artery descends on the interosseous membrane, innervating the tibialis anterior, extensor hallucis longus, and extensor digitorum longus muscles. The terminal portion of this nerve then passes under the extensor retinaculum at the ankle, where a lateral branch innervates the extensor digitorum brevis muscle and a medial branch provides sensory innervation to the first and second toes.

1. **Etiology.** Most cases of peroneal neuropathy are caused by external compression (anesthesia and casts), trauma (blunt injury, arthroscopic knee surgery, and fractures) and less frequently by other etiologies (e.g., tumor, constriction by adjacent structures, involvement in systemic disease, and traction injuries from severe ankle strain).
2. **Clinical manifestations.**
   a. **History.** Most patients present with foot-drop, and sensory disorders are usually minimal or of no concern. Less prominent degrees of weakness or only affecting intrinsic foot muscles may not elicit alarm in the patient. On review of the history, careful attention needs to be paid to possible episodes of trauma, compression, or unusual sustained postures that may have preceded the problem (e.g., squatting and kneeling).
   b. **Physical examination.**
      (1) **Neurologic.** The characteristic presentation is foot-drop, and with complete involvement of the common peroneal nerve, paralysis of ankle dorsiflexion, ankle eversion, and toe extension (dorsiflexion). Sensory loss occurs over the anterolateral lower leg and the dorsum of the foot and toes.
      (2) **General.** Palpation in the popliteal fossa and along the fibular head may elicit signs of tenderness or discovery of a mass and define the site of involvement and possible etiology. Examination of the dorsum of the ankle and distal lateral leg, where the terminal branch of the deep peroneal nerve emerges, may reveal similar signs and suggest a distal injury. The most common sites at which focal pathologic processes can affect the nerve or its branches include the fibular

head and its proximal neck, the outer compartment of the leg, and the superior and inferior extensor retinaculum at the ankle, beneath which branches of the peroneal nerve pass. However, the peroneal nerve serves as a reminder that, in cases of focal compression, there can be variable fascicular involvement. Motor impairment of only the deep or superficial component, sensory dysfunction only, or various combinations may be the result of nerve compression at the fibular head.

3. **Differential diagnosis.** The primary differential diagnoses are other causes of foot-drop: involvement of the L5 root, the lumbosacral trunk, and the lateral division of the sciatic nerve.
4. **Evaluation.** The extent of evaluation depends on the history. In cases in which an identifiable episode of compression is present, supportive care, after elimination of continuing compression, is often all that is needed. When disruption (laceration) of the nerve is suggested, the onset of the problem is insidious, or physical findings are inconclusive (incomplete common peroneal neuropathy), further evaluation is indicated.
   a. **Electrodiagnostic.** NSS assist in identification of the site of involvement, extent of axonal injury and prognosis by comparison to the asymptomatic leg, but could identify bilateral, although asymmetric, nerve involvement suggesting an underlying generalized nerve disorder (polyneuropathy). EMG helps to further define the extent of axonal injury or evidence of etiology of the patient's symptoms, if abnormalities are found in other L4–5 innervated muscles or paraspinal muscles.
   b. **Imaging.** Although X-ray studies can be useful when joint trauma or a mass is detectable at examination, CT and MRI are more useful in defining lesions of the nerve and delineating the relationship of adjacent structures.

F. Tibial neuropathy. Ventral rami from the L5 to S2 spinal nerves contribute to the tibial nerve, which descends into the extremity as part of the medial trunk of the sciatic nerve. At the distal portion of the extremity, the sciatic nerve bifurcates into both the tibial and peroneal nerves. Entering the calf, it descends to the depth of the gastrocnemius, which it innervates, and provides innervation to the soleus, tibialis posterior, flexor digitorum, and hallucis longus muscles. At the level of the ankle, it divides into its terminal branches (plantar nerves), which innervate all intrinsic foot flexor muscles as well as providing sensation to the sole.

1. **Etiology.** Tibial neuropathy is infrequent partly because of the deep anatomic location of the nerve but, severe ankle injuries can cause proximal or distal tibial nerve injuries through traction on the nerve. Major knee trauma is surprisingly an infrequent cause of severe tibial nerve injury.
2. **Clinical manifestations.**
   a. **History.** Sensory loss is evident along the side of the foot and extends proximally if the contribution of the tibial nerve to the sural nerve is also involved. Weakness may not be noticed unless ankle plantar flexion is involved.
   b. **Physical examination.**
      (1) **Neurologic.** Sensory loss is present along the sole of the foot. Weakness may be limited to intrinsic toe flexor muscles, or, with more proximal muscle involvement, weakness of ankle dorsiflexion and inversion.
      (2) **General.** Careful palpation over the course of the nerve, especially within the popliteal space, should be performed. The finding of a mass or precipitation of paresthesia or pain helps in localization and may suggest the cause as tumors involving the tibial nerve (or any nerve) may increase their sensitivity to such maneuvers.
3. **Differential diagnosis.** Because of its infrequent occurrence, any suspicion of tibial neuropathy should prompt a search for a more proximal lesion. Radiculopathy, plexopathy, or sciatic neuropathy can manifest clinically as an "isolated" tibial neuropathy. Careful examination of more proximal muscles, reflexes, as well as the sensory examination can help identify or suggest those conditions as more appropriate diagnoses.
4. **Evaluation.**
   a. **EDS** play a crucial role in identifying as well as excluding a tibial neuropathy by identifying involvement of other nerves on NSS or EMG evidence of muscle involvement other than those innervated by the tibial nerve. At times, plantar nerve

involvement rather than a more proximal tibial lesion is the cause of the observed sensory or motor deficits.

b. **Imaging.** Identification of a mass or point of tenderness in cases of unclear causation may necessitate MRI to identify the anatomic structure of the nerve and its relations to adjacent structures.

G. Medial and lateral plantar neuropathy. At the level of the ankle, the terminal portion of the tibial nerve is medial to the Achilles tendon. As it descends, it passes under the flexor retinaculum, which composes the roof of the tarsal tunnel. Within the tunnel, the tibial nerve divides into medial and lateral plantar nerves, which descend toward the foot, and a calcaneal or sensory branch, which provides sensation over the heel. Both plantar nerves then cross under the abductor hallucis muscle (which the medial plantar nerve innervates) and go on to innervate all the muscles of the foot as well as providing sensation to the sole and the toes (the medial nerve supplies the medial and the lateral supplies the lateral portion) through their distal divisions, which give rise to the digital nerves. Muscles innervated by the medial plantar nerve include the flexor hallucis brevis and digitorum brevis. The lateral plantar nerve innervates the interossei, the flexor and abductor digiti minimi, and the adductor hallucis.

1. **Etiology.** The proximity of the plantar nerves to osseous and fibrous structures predisposes them to injury or compression. At the level of the tarsal tunnel, external compression and ankle injury are the most frequent etiologic factors. A multitude of other less frequent structural abnormalities (synovial or joint changes and mass lesions) can also lead to nerve injury. Within the foot itself, the medial and lateral plantar nerves are susceptible to the effects of trauma or fracture of the foot bones.
2. **Clinical manifestations.**
   a. **History.** The first recognition of disorder occurs when sensory impairment develops, because foot pain or discomfort more frequently has an orthopedic origin. Sensory loss can be present in the sole or heel and at times can be precipitated by specific foot positions. Weakness of foot muscles usually produces no significant symptoms.
   b. **Physical examination.**
      (1) **Neurologic.** Sensory loss in the distribution of the plantar nerves or their distal divisions (digital nerves) should be sought. If foot involvement is asymmetric, changes in foot muscle bulk can be appreciated, as can weakness, although usually only toe flexion can be reliably evaluated clinically.
      (2) **General.** Careful examination of the course of the nerve at the ankle and attempts to elicit a Tinel's sign by means of light percussion over its course help confirm the presence and location of plantar nerve involvement. Joint changes, deformity, or swelling can also help to suggest a site of nerve involvement.
3. **Differential diagnosis.** One needs to consider a more proximal nerve (tibial) or root (S1) lesions that can cause foot pain or paresthesia. Motor and reflex changes should aid in this distinction. Polyneuropathy can be considered when bilaterality, depressed reflexes, and sensory involvement outside of the plantar sensory nerve distribution are found.
4. **Evaluation.**
   a. **EDS** are helpful in demonstrating findings consistent with nerve entrapment (tarsal tunnel) of the medial or lateral plantar as well as calcaneal nerves. Because of the technical difficulty of such recordings, further study of asymptomatic or contralateral nerves clarifies the findings. An EMG is needed to exclude more proximal disorders (tibial neuropathy, sciatic neuropathy, or radiculopathy).
   b. **Imaging.** Studies of possible sites of involvement (ankle) are not usually indicated. However, in cases of marked discomfort or disability, such studies may identify underlying orthopedic abnormalities and guide treatment.

H. Iliohypogastric, ilioinguinal, and genitofemoral neuropathy. The iliohypogastric, ilioinguinal, and genitofemoral nerves are described as a group because of the similarity of their origins, sensory innervation, and causes of dysfunction. These nerves arise from the L1 spinal roots (the genitofemoral nerve also has an L2 root contribution) and first pass through and then close to the psoas muscle in their intraabdominal course. The iliohypogastric nerve emerges above the iliac crest and supplies sensation to an area of skin over the lateral upper buttock and another area over the pubis or symphysis.

The ilioinguinal nerve enters the inguinal canal at its lateral border and supplies the area above the inguinal ligament and the base of the genitalia. Both the iliohypogastric and ilioinguinal nerves also supply the muscles of the lower abdominal area. Clinically evident weakness of the lower abdominal musculature can occur, but perhaps more common with loss of function of both of those nerves. After it emerges from the psoas muscle, the genitofemoral nerve is retroperitoneal and descends to the inguinal ligament while resting on the surface of the psoas muscle. It supplies sensation to a small area over the proximal genitalia and anterior proximal thigh.

1. **Etiology.** Because of the location and course of these nerves, neuropathy usually results from surgical procedures, especially inguinal herniorrhaphy. The development of neuralgia is not infrequent after injuries to these nerves.
2. **Clinical manifestations.**
   a. **History.** Patients have varying sensory problems, including numbness, paresthesia, or pain within the ipsilateral inguinal and perineal areas. If the cause is related to surgery, these difficulties may be evident immediately after the operation or may not become evident for several weeks.
   b. **Physical examination.**
      (1) **Neurologic.** Iliohypogastric neuropathies are infrequent, but result in sensory loss over the lateral upper buttock and suprapubic area. Ilioinguinal impairment results in sensory loss over the inguinal area and the base of the genitalia but typically resolves or results in minimal disability. In other cases, pain may appear both here and in the inferior abdomen and upper thigh and be worsened or precipitated by changes in leg position. Genitofemoral neuropathy usually accompanies inguinal nerve involvement because of the anatomic proximity of the genitofemoral and inguinal nerves. Symptoms and precipitating factors are similar as well, but sensory problems can extend into the medial and proximal areas of the genitalia.
      (2) **General.** In ilioinguinal and genitofemoral neuropathy, areas of tenderness that often conform to the site of injury may be found in the inguinal region.
3. **Differential diagnosis.** In these cases, nerve involvement predominantly causes sensory impairment, and the differential diagnosis is directed at detecting other causes of sensory impairment outside the typical boundaries of these nerves, including abnormalities in the medial thigh (obturator nerve), anterior thigh (femoral nerve), and lateral thigh (lateral femoral cutaneous nerve), as well as dermatomal involvement caused by T12 or L1 radiculopathy. Because of these overlapping sensory innervations, the presence of motor deficits or reflex changes provides the strongest clue to the presence of one of these other disorders. Back pain, which can suggest a radiculopathy, or the absence of a previous operative procedure, which is the usual cause of these neuropathies, suggests another etiologic factor.
4. **Evaluation.**
   a. **EDS** play little role in the identification of these neuropathies. However, they become indispensable in helping to identify more proximal lesions (plexus or root) or other forms of neuropathy (femoral) that may clinically resemble iliohypogastric, ilioinguinal, or genitofemoral neuropathy in regard to sensory deficits.
   b. **Imaging** is performed if there is suspicion of radiculopathy or if a retroperitoneal, intraabdominal, or pelvic lesion is under consideration.

I. Miscellaneous neuropathy. This grouping and brief review is based on their infrequent occurrence or isolated involvement.

1. **Superior gluteal neuropathy.** Arising from, and receiving its contributions from the L4 to S1 components of the sacral plexus, the nerve passes through the sciatic notch above the piriformis muscle and innervates the gluteus medius and minimus muscles. Its isolated involvement is unusual and is most often the result of injury by a misplaced injection.
2. **Inferior gluteal neuropathy.** Arises from the L5 to S2 divisions of the sacral plexus and exits through the sciatic notch. Its proximity to the sciatic, pudendal, and posterior cutaneous nerves of the extremity results in concomitant injury to these nerves.
3. **Posterior cutaneous nerve of the thigh.** Arising from the S1 to S3 components of the sacral plexus, it descends through the sciatic notch close to the sciatic nerve and supplies

sensation to the posterior portion of the buttock and thigh. At times it is susceptible to local compression, but its isolated involvement is unusual.

4. **Pudendal neuropathy.** Derived from the S2 to S4 components of the sacral plexus, it passes through the sciatic notch and descends toward the perineum. Supplying muscles of the perineum, including the anal sphincter and erectile tissue, it also provides sensory innervation to the perineum. Its deep location protects it, but prolonged compression can cause dysfunction or stretch injuries related to prolonged labor and manifested by fecal and urinary incontinence.

III. REFERRALS

A. Indications for and purposes of neurologic consultation.

1. Site of involvement unclear from examination or history, discrepancy between severity of the underlying disease and the neuropathy.
2. Progressive deterioration despite appropriate treatment.
3. Problem precipitated by trauma or injury.
4. Prior to more expensive or invasive evaluation (MRI or nerve biopsy) or more aggressive intervention (surgery).
5. Confirmation of diagnosis, etiologic factor, or treatment plan.

B. EMG and NSS evaluation.

1. Basic tenets of such testing.
   a. Extension of the clinical examination and not a replacement.
   b. Intended to clarify the clinical question to be answered (e.g., carpal tunnel syndrome or C6 radiculopathy).
   c. Sensitivity and specificity vary according to the etiologic factor and process in question.
2. Role in the evaluation of neuropathy.
   a. Confirmation of diagnosis or characterization, localization, and quantification of a disease process.
   b. Defining prognosis.
   c. Detection of subclinical disease.
   d. Planning treatment or determining need for further evaluation or consultation.

Recommended Readings

Brazis PW, Masdeu JC, Biller J. *Localization in Clinical Neurology*. 6th ed. New York, NY: Lippincott Williams & Wilkins; 2011.

Donovan A, Rosenberg ZS, Cavalcanti CF. MR imaging of entrapment neuropathies of the lower extremity. Part 2. The knee, leg, ankle and foot. *Radiographics*. 2010;30:1001–1019.

O'Brien M. *Aids to the Examination of the Peripheral Nervous System*. 5th ed. New York, NY: W.B. Saunders; 2010.

Petchprapa CN, Rosenberg ZS, Sconfienza LM, et al. MR imaging of entrapment neuropathies of the lower extremity. Part 1. The pelvis and hip. *Radiographics*. 2010;30:983–1000.

Preston DC, Shapiro B. *Electromyography and Neuromuscular Disorders: Clinical-Electrophysiologic Correlations*. 2nd ed. Philadelphia, PA: Butterworth-Heineman; 2005.

Stewart JD. *Focal Peripheral Neuropathies*. 4th ed. West Vancouver: JBL Publishing; 2010.

CHAPTER

26 Approach to the Patient with Failed Back Syndrome

Russ P. Nockels and Michael W. Groff

Although commonly used as a diagnostic term, failed back syndrome (FBS) is a misnomer. The term "syndrome" should not be applied to patients with a "failed back" because it gives the perception that patients with FBS have a group of symptoms that commonly occur together. Taken as such, the danger exists that a clinician may disregard important signs and symptoms that will lead to the proper treatment of a patient. Fortunately, a set of diagnostic principles can be used to clarify these issues and, from a practical standpoint, be used methodically to achieve a more appropriate diagnosis.

I. FAILED BACK SYNDROME

The FBS is a clinical condition experienced by patients who undergo a surgical procedure, typically in the lumbosacral region, with unsatisfactory results. Back pain is the second most common reason, behind asthma, for patients to seek medical help. It has been estimated that 300,000 laminectomies were performed last year. With the advent of modern instrumentation systems, an increasing number of lumbar fusions are being performed each year. Unfortunately, not every operation is successful, the success rate ranges from 50% to nearly 100% depending on the indication. Consequently, the prevalence of FBS is quite high.

Categories of FBS include the following:

A. Failure to improve due to misdiagnosis. By definition, FBS implies previous surgery. Therefore the first priority in the evaluation of these patients is to understand the indication for the original operation. It is often helpful to ask the patient to compare current symptoms with those experienced prior to surgery in terms of location, frequency, and intensity. A patient who fails to improve at all following surgery is more likely to have been misdiagnosed than a patient who improves for a period of time. If the original indication for surgery is suspect, it is extremely unlikely that further surgical intervention will be helpful.

B. Failure to improve due to improper treatment. Patients who do not improve or worsen immediately after surgery may have suffered a technical error during surgery. These errors include inadequate decompression, wrong level surgery, or nerve root injury. Frank instability of the operated level may also worsen if an unstable spinal motion segment such as a mobile spondyllolisthesis is not stabilized or fused at the time of decompression.

C. Recurrent pathology. A patient who experiences identical recurrent symptoms after a postoperative period of significant improvement will likely harbor recurrent pathology. Disc herniations, for example, carry a lifelong risk of recurrence because the majority of the anatomical intervertebral disc remains after a discectomy and the annular tear that permits the herniation never completely heals. An infection may also be present, frequently becoming apparent within the first 4 weeks of surgery. Infections may cause recurrent symptoms as well as the new onset of significant back pain. These infections can be occult, and imaging studies should be performed to determine if endplate erosion or a fluid collection is present.

D. Progression of pathologic changes at unoperated sites. Surgical procedures of the lumbar spine are commonly performed for degenerative diseases. Spondylosis, or bony overgrowth of the facet joints and intervertebral endplates, in association with soft tissue ligamentous hypertrophy can cause significant stenosis. Spondylolisthesis, or malalignment of the spine, can progress after decompression alone, causing recurrent nerve root entrapment. Additionally, progression of degenerative changes at a level adjacent to a lumbar fusion may occur, resulting in stenosis and/or spondylolisthesis.

II. SIGNS AND SYMPTOMS THAT WILL AID IN THE ASSESSMENT OF FBS

A. Radiculopathy is a pain that shoots like a jolt of electricity and follows a particular dermatomal distribution. This is most often caused by a herniated disk, but not exclusively so. Many times there is associated sensory loss in the same dermatome. The associated myotome can manifest weakness in some cases. Abnormal reflexes can also help to localize the level of involvement in the spinal canal.

1. Imaging is helpful in this context to confirm the level implicated by the history and physical examination findings. However, it has been well-shown that healthy persons without back pain can harbor disks that would be concerning from a purely radiographic perspective. Therefore, imaging findings without a clinical correlate can typically be ignored.
2. The most common cause of the pathogenesis of radiculopathy is herniation of a disk followed closely by degenerative foraminal stenosis. Other entities, such as synovial cyst, are distinctly less common.
3. Whatever the cause, surgery for radiculopathy is focused on decompressing the affected nerve root. The prognosis is quite good; early good results are achieved in >95% of cases.
4. When this type of surgery is unsuccessful, strong consideration should be given to the possibility that the diagnosis was incorrect, the wrong level was operated on, or the patient has secondary issues that are preventing improvement.
5. Radiculopathy can be confused with hip disease in some cases. A positive **Patrick's test** should be followed with an evaluation to rule out hip arthrosis.

B. Claudication is a cramping pain or sense of fatigue in the legs caused by exertion. Most patients report the onset of symptoms after walking a particular distance. The pain typically abates after several minutes of rest, such that the person can continue.

1. It is important not to confuse **neurogenic** and **vascular** claudication. Patients with neurogenic claudication exhibit a "shopping cart sign," which is the ability to walk further when leaning forward. This flexed position slightly diminishes the ligamentous compression of the cauda equina, allowing the patient to walk further. For the same reason, a patient with neurogenic claudication will do much better on exercising bicycle than they would on walking. Patients with vascular claudication show no such improvement.
2. **Neurogenic claudication** is most commonly managed with lumbar laminectomy over the stenotic levels. The goal of surgery is to decompress the thecal sac by removing hypertrophied ligamentum flavum, the medial facet, and occasionally disc material. Foraminotomies are required to decompress the exiting nerve roots, and this may result in iatrogenic instability causing some patients to require fusion as well.
3. Imaging with either MRI or **CT myelography** shows a markedly compressed thecal sac with a characteristic trefoil configuration and amputation of the exiting nerve root sleeves.

C. Instability is another common indication for lumbar surgery. From both a theoretical and a practical standpoint, instability is distinct from stenosis and radiculopathy. Management of radiculopathy and stenosis is decompression; management of instability is fusion. The success of fusion operations is distinctly less than that of decompression. For this reason, many patients with FBS have experienced failed fusion.

1. **Instability** is defined as the ability of the bony components of the spine to withstand physiologic loads without mechanical pain or compromise of nerve root function.
2. Although instability often is thought of in a binomial way as either present or absent, in clinical practice there is a spectrum of instability ranging from **gross instability,** most often the result of trauma, to **microinstability,** which is found in the context of degenerative disease.
3. The underlying hypothesis in offering fusion to patients with degenerative spondylosis is that instability represents a painful dysfunctional motion segment. The pain is characteristically exacerbated by prolonged sitting or standing and often is relieved by recumbency. Because the pain does not radiate, it is not possible to localize the responsible spinal level by means of history or physical examination.

4. The pathogenesis of mechanical back pain is controversial and likely is multifactorial. There is evidence implicating the disk space as well as the facet joints. Many patients who improve after lumbar fusion fail to demonstrate overt instability on preoperative dynamic studies. Therefore, the specific pain generator is unknown, and the lumbar segment inclusive of the disc and facet joints is thought to be dysfunctional.
5. If **flexion–extension radiographs (dynamic radiographs)** show movement of >4 mm, the diagnosis is more certain. However, a large number of patients with movement in excess of 4 mm also do not have mechanical pain. Plain radiographs can provide indirect evidence of instability in the form of traction spurs that result from the tension placed on the bone from **Sharpy's fibers** of the annulus or loss of disk height indicative of disk degeneration. MRI often shows **Modic's changes** at the interspace thought to represent inflammatory reaction in the adjacent vertebral bodies secondary to disk disruption. Many of these findings are present in patients who are pain free, and therefore their utility is suspect.
6. In an attempt to better determine whether instability is present in a particular patient and whether it is responsible for the back pain being reported, several strategies have emerged. The trial use of a temporary **external orthosis** or percutaneous **pedicle screws** before surgical fusion has fallen out of favor.
   a. Use of diagnostic facet blocks targeting a spinal level thought to be unstable can be helpful. Epidural steroids, although clinically beneficial, are of no diagnostic significance because they are not specific to an anatomic level.
   b. **Provocative diskography** has been championed because it shows the disk disruption anatomically and functionally. Great care must be taken to inject both normal and diseased levels in a patient-blinded fashion in order to determine whether the targeted level(s) have pain concordant with the patient's primary complaints of back pain.
7. Technical aspects of lumbar fusion have improved outcomes such as the use of supplemental interbody devices, less rigid implants, and bone morphogenic protein (BMP). However, it is still not possible to predict who will benefit from lumbar fusion and who will not with a high degree of certainty. This explains, in part, the relative lack of success with fusion operations compared with decompression operations for radiculopathy or stenosis. Most series have favorable outcome in 50% to 70% of cases when lumbar fusion is performed for degenerative disease.
8. If the indication for fusion was not present at the time of the first operation, revision surgery will be futile. Moreover, even when the original procedure is well conceived, revision surgery is effective only if a problem amenable to surgical correction is identified preoperatively. Examples consistent with a successful operation include pseudoarthrosis and degeneration at the level adjacent to the fusion. The plan should be well defined preoperatively.

III. SOMATIC PROBLEMS NOT RELATED TO THE SPINE

Many somatic problems not related to the spine can manifest as back pain. These must be excluded in a thorough review of systems.

A. **Abdominal causes** include aortic aneurysm, cholelithiasis, and pancreatitis. Pyelonephritis most often manifests as flank pain but can also lead to referred back pain.
B. In female patients, **endometriosis** can manifest as low back pain.
C. **Sacroiliac joint (SIJ) pain** is increasingly common due to abnormal shifting of the pelvis in patients with lumbar degenerative disease. Injections of the SIJ can be both diagnostic and therapeutic.
D. **Osteoarthritis of the hip** can be easily confused with back pain radiating into the buttock. Patrick's test is useful to differentiate the two. Severe radiation of the pain to the groin is diagnostic of hip pathology.
E. **Major depression** has been shown to exacerbate the severity of back pain. It is also a poor prognostic sign for outcome after surgical intervention. Ongoing worker's

compensation litigation has also been shown to be an independent predictor of poor outcome.

IV. NONSURGICAL MODALITIES

After the rationale for the primary operation or previous operations is understood, emphasis should be given to nonsurgical modalities. In any cohort of patients with FBS, only a small number should ever come to revision surgery.

A. It should be well-understood that **lumbar spondylosis** is a degenerative disease. As such, surgery can ameliorate the most severe manifestations of the problem, but it can never address the underlying cause. For this reason, treatment such as weight loss, smoking cessation, and physical therapy offers the patient a better outcome, if successful, and can often make surgery unnecessary. Moreover, even when surgery is entertained, it should only be in the context of a complete treatment plan that embraces these other aspects of care. At the same time, the efficacy of surgery decreases with each subsequent operation, unless significant additional pathology has been uncovered.

B. Degenerative changes in the spine are often associated with deformities. These deformities can be focal such as spondylolisthesis, or more global, such as scoliosis. Recently, sagittal deformities have been demonstrated to have a significant impact on outcome. If these sagittal imbalances are fixed, that is, not amenable to postural changes by the patient, surgical correction of the deformity may be required. In the past, lumbar fusion surgeries focused less on sagittal issues and may have resulted in **flat back syndrome**, whereby the lumbar spine was fused in a hypolordotic position. Patients with FBS due to fixed sagittal imbalance require long cassette standing scoliosis studies to accurately assess the condition.

C. In most cases of FBS, the patient comes to medical attention with the chief symptom of pain. Pain is a subjective symptom. Considerable progress has been made in the development of **outcome instruments** (Oswestry, SF36) that attempt to quantify pain and functional level in an objective way. This has given spine specialists a means of comparing of the clinical effectiveness of various interventions.

D. The pain that patients report and the disability they experience have a great deal to do with their expectations. Pain is ordinarily an important protective phenomenon. When pain becomes chronic, as in FBS, the noxious percept that reaches consciousness serves no productive purpose. The assumption of many patients that the pain they are experiencing is evidence of ongoing damage is incorrect. When patients understand this, their perception of pain can become less noxious, and their functional abilities can improve. Therefore, patient education can play a therapeutic role.

E. As a clearer understanding emerges of the nature of pain in FBS, more effective, interdisciplinary treatments are being developed. It is increasingly recognized that depression not only exacerbates the symptoms of FBS but also is a consistent consequence of FBS. If relatively severe, depression should be addressed before surgical intervention is planned.

V. PAIN MANAGEMENT

The nonsurgical therapies discussed in **IV** address the causes of FBS in just as direct a manner as surgery does. In some cases, indirect measures can be considered purely with the intent of ameliorating a patient's pain. Although these modalities are not directed at the underlying cause, they do enhance functional ability and improve quality of life.

A. There is increasing experience with **narcotics** in the management of chronic pain of a nonmalignant causation, such as FBS. This is an expansion of experience with **cancer pain.** Subsequently, some authors have expanded the indications to include patients with **chronic pain of benign causation.** Because the life expectancy of patients with FBS is much longer than that of patients with cancer, the duration of treatment is

considerably longer. These patients must be followed for the development of toleration and habituation. Topical forms of opiates such as Fentanyl have been increasingly used for chronic pain because their pharmacokinetic profile lacks the peak and trough levels of oral opiates. Serum chemistries with liver function tests should be checked on a regular schedule. Moreover, it has been estimated that as many as 45% of patients with FBS are being medicated excessively, and this treatment remains controversial.

B. **Intrathecal pumps** for the administration of opioids have been used to minimize the side effects of systemic opiate therapy, such as sedation, lethargy, and decreased libido. Because the drug is delivered directly to the opiate receptors within the dorsal horn of the spinal cord, effective analgesia can be obtained at much lower doses. This leads to a much lower incidence of side effects. However, the use of intrathecal pumps has increasingly been reserved for patients with pain due to cancer, as oral and topical analgesics have become more effective.

C. The **gate-control theory** of pain proposed by Melzack and Wall was the inspiration for **spinal cord stimulation.** Modern implantable and rechargeable systems are much more effective and easier to insert than earlier versions. Most studies demonstrate favorable early and late success for these implants in treating FBS, although the cost effectiveness of these procedures is currently under debate. The complication rate is low, neurologic injury occurring in <1% of patients.

VI. SURGICAL MANAGEMENT

When conservative therapy is unsuccessful, operative intervention should be considered.

A. In cases of **immediate failure,** the patients never improve after surgery. This universally implies an **error in diagnosis** or a **technical deficiency** with the surgery. After the protocol outlined in **IV** and **V** has been implemented, these patients require MRI with and without contrast material. The prognosis for these patients is very good when an error is identified. If no deficiency is found, the outcome is considerably more discouraging. Surgery has no role in those cases.

B. The next group of failures manifests **days to weeks** after surgery. It is quite common, however, for patients who have initial improvement postoperatively in the hospital to experience a setback as they become more active on arriving home. This is a normal although not universal finding and is best managed expectantly. Patients who experience initial improvement and then experience clear deterioration need a more deliberate evaluation. These cases can represent **recurrent disk herniation**, **iatrogenic instability,** or **sagittal imbalance.** The physical examination and pain signature favor one diagnosis over the other. Recurrent nerve root compression is best evaluated with MRI with and without contrast material. Instability should be evaluated with CT to assess the bony removal, and dynamic plain radiographs. Standing long cassette studies in both the coronal and sagittal plane are required to rule out deformity. In this time frame, some patients have progressive **causalgia-type** or **neuropathic pain.** This may result from a prolonged preoperative duration of nerve compression or injury during surgery. This condition is very refractory, although recent success has been reported with Gabapentin and some antidepressants.

C. Another group of failures manifests **weeks to months** after surgery. The description of clear radiculopathy suggests recurrent herniation. **Arachnoiditis** manifests most often at this time. Patients often describe back and leg pain, which can be similar to the presenting problem. Classic cases manifest as symptoms of claudication or lower extremity causalgia. CT myelography is the study of choice and typically shows clumping of nerve roots and restricted flow of intrathecal contrast material. Surgery directed at the arachnoiditis is unsuccessful. There has been some success with spinal cord stimulators in these cases. Thankfully, the incidence has decreased dramatically with the advent of water-soluble contrast agents and the relatively infrequent use of myelography in the MRI era.

D. The last group of failures manifests after a pain-free interval of **months to years.**

1. Many of these cases have developed either iatrogenic lumbar instability because decompression was too wide or lumbar instability caused by the intrinsic disease. The incidence of **postlaminectomy spondylolisthesis** is somewhere between 2% and 10%. Even simple diskectomy has been associated with a 3% incidence of postoperative instability that necessitates subsequent fusion. It has been widely circulated that the medial half of the facet joint can be removed bilaterally without inducing instability. However, this admonishment is not consistent with the fact that the medial half of the joint comprises the descending facet almost exclusively and that removal of the medial half can leave the facet completely incompetent. There is consensus that complete laminectomy and bilateral facetectomy consistently produce instability. In cases in which this extent of resection is needed to accomplish decompression, fusion should be incorporated into the surgical plan.
2. **Pseudoarthrosis** after lumbar fusion manifests in a time frame similar to that of postlaminectomy spondylolisthesis. In part, the timing of presentation may represent the fact that most spine surgeons are not prepared to give up on a fusion for 9 to 12 months after surgery. There are also no commonly accepted criteria for diagnosis of pseudoarthrosis. Dynamic radiographs often appear normal, and bone scans are equivocal. The incidence of symptomatic pseudoarthrosis after a posterolateral lumbosacral fusion is between 5% and 15%. The cause can be either technical deficiency of the surgery or biologic deficiency of the patient. There is good evidence that smoking negatively affects the rate of fusion. The rate of pseudoarthrosis increases with the number of levels of arthrodesis. The use of BMP, external bone stimulators, and the use of allograft bone graft extenders have decreased the rate of pseudoarthrosis. Hardware implanted in the patient may also become symptomatic during this time frame. The modulus of elasticity of metal rods is 10 to 20 times stiffer than bone, so that even following a successful fusion, these implants may loosen at the bone-implant interface or break. Recent experience suggests alternate biomaterials, such as PEEK, may be a more suitable implant due to a its near identical stiffness to bone, and resistance to breakage.

VII. RADIOGRAPHIC EVALUATION OF FBS

Radiography plays an important role in the evaluation of FBS.

A. In the evaluation of recurrent disk herniation, **contrast-enhanced CT** or **MRI** is vital (Figs. 26.1 and 26.2). Postoperative scar becomes homogeneously enhanced. A herniated disk may have some peripheral enhancement, but because it is avascular, the disk does not become centrally enhanced. Although scar and disk can both cause compressive symptoms, surgery to remove scar tissue is rarely successful.

B. Radiographic evaluation of a fusion is more difficult. In short, there is no universally accepted way to assess successful fusion after arthrodesis.

1. **Dynamic** or **flexion and extension radiographs** are specific for instability if motion is detected. However, these studies are very insensitive. Fibrous nonunion or the instrumentation itself can prevent the flexion–extension radiographs from appearing abnormal.
2. **Plain radiographs** can show a robust fusion mass, but it is often impossible to know whether the bony mass is in continuity. Lucency or halos around pedicle screws suggest instability. CT with sagittal and coronal reconstruction can be helpful. Special techniques must be used to minimize artifact of the instrumentation.
3. **Bone spectroscopy** has been advocated, but this modality is unreliable for at least several years after surgery.
4. **Three-dimensional CT** has been advocated by some authors in the evaluation of FBS. It has the advantage of clearly imaging the bony resection and can clearly delineate the extent of bony fusion.

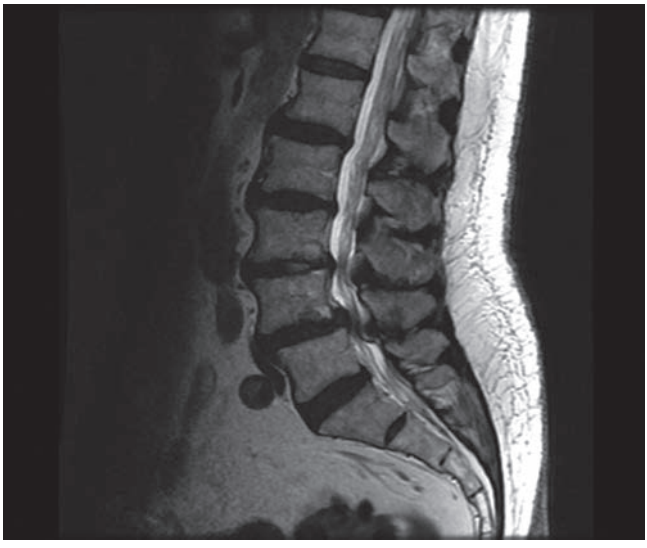

FIGURE 26.1 Preoperative lumbar MRI showing stenosis at L3–5 with an L4–5 spondylolisthesis.

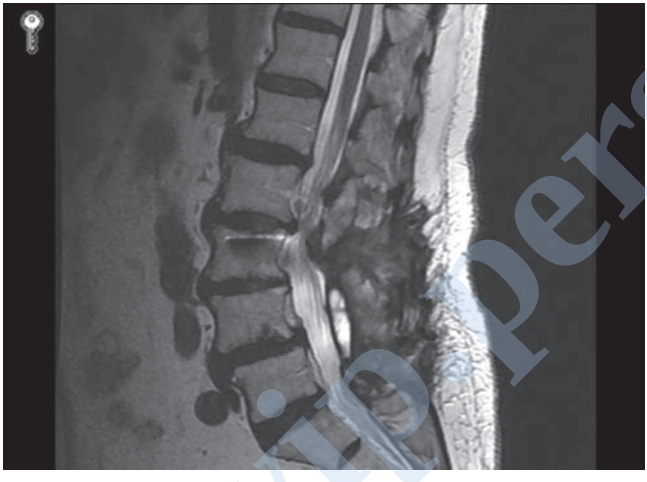

FIGURE 26.2 Repeat lumbar MRI obtained 3 years following L3–5 laminectomies and fusion, and recurrent symptoms. Note junctional stenosis at the L2–3 level.

VIII. REFERRALS

A. Referral to a neurologist or spine surgeon is indicated for any patient with a new or progressive neurologic deficit. In the context of FBS and chronic pain, it is important not to miss this dramatic change in the patient's course.

B. Imaging should be performed only in response to a significant change in the symptoms. When dramatic changes are found at imaging studies, patients with FBS should be reevaluated.

C. Often the job of weaning narcotics is left to an internist or general neurosurgeon. This can be appropriate; however, when reduction goals are not being met and the program

becomes stalled, these patients should be referred to specialized centers. Long-term use of narcotic analgesics can be acceptable treatment in some cases, but it should be chosen explicitly, not as an ad hoc default.

D. FBS is a difficult management problem, and all these patients should be seen by a spine surgeon or pain center. In general, patients with FBS should be cared for by a multidisciplinary team. It is important to maintain vigilance in case new important symptoms arise which may alter the treatment regimen.

Recommended Readings

Burton AK, Waddell G, Tillotson KM, et al. Information and advice to patients with back pain can have a positive effect. *Spine*. 1999;24:2484–2491.

Chou R. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. *Spine*. 2009;34:1078–1093.

Frey M, Manchikanti L, Benyamin R, et al. Spinal cord stimulation for patients with failed back surgery syndrome: a systematic review. *Pain Physician*. 2009;12:379–397.

Jee-Soo J, Sang-Ho L, Jun-Hong M, et al. Surgical treatment of failed back surgery syndrome due to sagittal imbalance. *Spine*. 2007;32:3081–3087.

Line J. Spinal cord stimulation versus conventional medical management for failed back surgery syndrome: long-term results from the PROCESS study. *Neurosurgery*. 2008;62:1426–1427.

Melzack R, Wall PD. *The Challenge of Pain*. New York, NY: Basic Books; 1983.

Van Buyten J, Linderoth B. "The failed back surgery syndrome": definition and therapeutic algorithms—an update. *Eur J Pain Suppl*. 2010;4:273–286.

Weinstein J, Lurie JD, Tosteson TD, et al. Surgical versus nonoperative treatment for lumbar disc herniation. *Spine*. 2008;33:2789–2800.

Weinstein J, Lurie JD, Tosteson TD, et al. Surgical compared with nonoperative treatment for lumbar degenerative spondylolisthesis. *J Bone Joint Surg*. 2009;91:1295–1304.

CHAPTER

27 Approach to the Patient with Acute Sensory Loss

David H. Mattson and Oldrich J. Kolar

Evaluation of **acute sensory loss** involves clinical assessment of the nature of the sensory loss (Section I), localization of the pathologic process (Section II), association of other neurologic signs (Section III), evaluation of possible etiologies (Section IV), and diagnostic testing (Section V).

I. CLINICAL MANIFESTATIONS

The location, extent, and quality of the sensory deficit can help to localize the lesion and narrow the differential diagnosis, keeping in mind that often no sensory impairment can be found in persons reporting acute sensory disturbances. Conversely, the neurologic examination may show sensory deficits of which the patient is unaware.

A. Examination of sensory modalities in acute sensory loss.

1. Touch sensation is tested with a wisp of cotton or the light touch of a finger. The stimulus should be compared with that applied to the contralateral corresponding area with expected normal sensation.
2. **Pain sensation** is tested by indicating the intensity of the pinprick sensation in comparison with that in a corresponding area with normal pain sensation.
3. It must be determined if an area of decreased sensation suggests **nerve root** or **peripheral nerve** involvement. Dermatomal charts showing typical peripheral nerve or nerve root distributions vary somewhat from one book or study to another, and there can be variability among patients. Should the pinprick sensation indicate a decrease or loss of pain sensation at a certain level of the chest or abdomen, the level is determined more reliably by proceeding from the area of decreased or absent sensation to the area of normal sensation.
4. **Position sense** in fingers or toes is examined by holding the digit at the side opposite to the direction of movement. The patient is asked to identify the directions of passive flexion and extension.
5. **Vibration sense** is a composite sensation requiring preserved touch and deep pressure sensation. A 128-dv tuning fork should be used and placed over a boney prominence.

B. Positive sensory symptoms.

1. **Paresthesia** means spontaneous abnormal sensation frequently described as tingling, prickling, or "pins and needles."
2. **Dysesthesia** is discomfort or pain triggered by normally painless stimuli.
3. **Hyperesthesia** indicates abnormally increased sensitivity to light touch, pinprick, or thermal sensation.

C. Negative sensory symptoms.

1. **Numbness** indicates decreased or absent sensation.
2. **Anesthesia** is complete loss of sensation.
3. **Hypesthesia** is decreased sensation.
4. **Pallesthesia** indicates loss of vibratory sensation.

D. Functional sensory loss. It often is difficult to establish with certainty that sensory impairment is functional, meaning inorganic or nonphysiologic. Functional sensory loss frequently occurs in a nonanatomic distribution, but so can CNS inflammatory demyelinating sensory loss. Losses of touch, pinprick, and vibration sensation exactly at the midline over the chest or abdomen, or in the entire limb with sharp delineation of the sensory loss, or poor reproducibility of the demarcation of the sensory deficits with repeated exams, all suggest functional sensory loss.

II. LOCALIZATION OF THE PATHOLOGIC PROCESSES

Localization of the pathologic processes resulting in acute sensory loss can be helpful in differential diagnostic considerations and in the selection of proper paraclinical investigations.

A. Sensory receptors.

1. **Exteroceptors** are localized in the skin and subserve superficial sensation to pain, touch, and temperature. The cutaneous sensory fibers run in sensory or mixed sensory and motor nerves. Sensory neurons have their cell bodies in the dorsal ganglia with their central projections to the posterior roots.
2. **Proprioceptors** are localized in deeper somatic structures, including tendons, muscles, and joints, dorsal columns of the spinal cord, and terminate in the gracile and cuneate nuclei of the medulla. The secondary afferent fibers from these nuclei cross the midline in the medulla and ascend in the brainstem as the medial lemniscus to the posterior thalamic complex. Proprioceptive information is carried through the spinocerebellar tracts in the lateral columns and in the cuneocerebellar and rostrocerebellar tracts in the dorsal columns of the cord.

B. Nerve roots. Individual nerve roots mediate sensation in segments oriented longitudinally in the extremities and horizontally over the trunk. Dermatomal charts depict typical nerve root distributions, but distributions vary from one study or book to another, and there can also be variability among patients.

C. Peripheral nerves. Dermatomal charts depict typical peripheral nerve and nerve bracnh distributions, but distributions vary from one study of book to another, and there can also be variability among patients.

D. Brachial and lumbosacral plexus. Acute sensorimotor deficits indicating multiple nerve or nerve root involvement in an arm or leg suggest plexopathy.

E. Spinal cord. Most fibers conducting pain and temperature sensation decussate over several segments by way of the ventral white commissure and ascend in the lateral columns of the cord as the lateral spinothalamic tract. Fibers conducting light touch and two-point discrimination ascend in the ipsilateral posterior column of the spinal cord and decussate in the medial lemniscus of the medulla.

F. Cranial nerve and brainstem. Cutaneous sensation from the face is carried to the brainstem by the trigeminal nerve. After entering the pons, part of the sensory fibers descend as a bundle to form the spinal tract of the trigeminal nerve, which reaches the upper cervical segment of the spinal cord. The spinal tract of the trigeminal nerve gives off fibers to the medially located nucleus of the spinal tract of the trigeminal nerve, which also descends into the upper cervical cord. The nucleus of the spinal tract of the trigeminal nerve receives fibers conducting sensations of pain, temperature, and light touch from the face and mucous membranes. Ascending fibers from the spinal nucleus travel mainly ipsilaterally in the trigeminothalamic tract and terminate in the ventral thalamus. The spinothalamic tract has connections with the brainstem reticular formation. It joins the medial lemniscus at the midbrain level and terminates in the posterior ventral complex of the thalamic nuclei.

G. Cortex. The cortical projections of the posterior ventral thalamic complex ascend through the medial portion of the internal capsule to reach the post-central cortex in a somatotopic arrangement with the face in the lowest area and the leg in the parasagittal region. In addition to the post-central cortex, the cortical thalamic projections include the superior parietal lobule, which is considered to represent sensations of numbness and tingling over the contralateral or bilateral aspects of the body. The fine sensory discrimination and fine location of pain, temperature, touch, and pressure (so-called primary modalities) require normal functioning of the sensory cortex. The cerebral cortex of the post-central gyrus also subserves cortical sensory processes, including perception of sizes and shapes of objects (stereognosis), ability to recognize numbers or letters drawn on the patient's skin (graphesthesia), and two-point discrimination.

III. CLINICAL ASPECTS OF ACUTE SENSORY LOSS BY SOMATOTOPIC LOCALIZATION

Pure sensory loss is unusual. Accompanying signs referable to brainstem, motor loss, associated cortical signs, and reflex abnormalities can help localize a lesion and narrow the diagnostic considerations and evaluation.

A. Acute sensory disturbance in the face usually indicates a lesion in a branch or branches of the trigeminal nerve, the trigeminal nucleus in the brainstem, or in the lemniscal pathways of the brainstem. It would be less typical to have pure facial sensory disturbance from a lesion in the thalamus, cortical projections, or somatosensory cortex (see III.B). Involvement of the ophthalmic branch of the trigeminal nerve can also cause a decreased blink reflex.

1. **Acute onset of facial paresthesia** manifesting as numbness, tingling, or ill-defined discomfort, if lasting only several seconds or minutes in a person who is exposed to stressful circumstances, is often idiopathic and self-limited. Paresthesia in the perioral area can be caused by and reproduced by hyperventilation. A severe form of lancinating facial pain can be very focal and feel like an abscessed tooth if in the mandibular branch of the trigeminal nerve, also known as tic douloureux, can also be idiopathic. Recurrent or chronic frontal or maxillary sinusitis can cause numbness referable to the ophthalmic or maxillary branches of the trigeminal nerve. Sensory disturbance in the maxillary division of the trigeminal nerve, which then spreads to the entire half of the face, suggests inflammatory demyelination. Sensory disturbance in the area of the mandibular division of the trigeminal nerve can reflect inflammatory or traumatic events involving the mandible or fracture of the base of the skull in the area of the foramen ovale. Relatively abrupt onset of sensory disturbance in the area of the chin suggests neuritis affecting the mental nerve and can be caused by osteomyelitis or the **numb chin syndrome** as a paraneoplastic manifestation of lymphoma, breast or prostate cancer, or melanoma.
2. Numbness or abnormal sensation can occur over the paretic facial muscles of **idiopathic peripheral facial nerve (Bell's) palsy.**
3. Alteration in sensation in the ophthalmic division of the trigeminal nerve and accompanying abrupt onset of fever, proptosis, chemosis, diplopia, and papilledema suggests **cavernous sinus thrombosis,** which can be caused by suppurative processes involving the upper half of the face, orbits, or nasal sinuses. Septic cavernous sinus thrombosis represents a life-threatening process necessitating immediate hospitalization. Sensory deficit in the ophthalmic division of the trigeminal nerve can also accompany acute onset of meningitis.
4. A relatively sudden onset of numbness over the first two divisions of the trigeminal nerve can result from a low-grade inflammatory process involving the cavernous sinus **(Tolosa–Hunt's syndrome),** which also causes lateralized retroocular or periorbital pain and diplopia secondary to involvement of the abducens nerve in the lateral wall of the cavernous sinus.

B. Facial sensory disturbance in association with hemibody sensory disturbance, either ipsilateral or contralateral.

1. Abrupt onset of hypalgesia and thermoanesthesia over the entire half of the face accompanied by hypalgesia and thermoanesthesia over the contralateral half of the trunk and extremities indicates involvement of the lateral medulla. The acute sensory loss often is associated with dysphagia, dysarthria, vertigo, vomiting, ipsilateral cerebellar signs, and ipsilateral Horner's syndrome. The most frequent cause of the lateral medullary (Wallenberg's) syndrome is occlusion of the intracranial vertebral artery. Less common causes include vertebral artery dissection, hematoma, demyelination, metastatic disease, and abscess.
2. Acute onset of bilateral or unilateral facial numbness rapidly extending into the contralateral half of the face and associated with or followed by progressive weakness of facial muscles can be the earliest manifestation of acute demyelinating polyneuropathy or **Guillain–Barré's syndrome (GBS)**. Cases that begin in the face and descend are called the **Fisher's variant of GBS.** Typical GBS starts with numbness, paresthesia, and weakness in the distal portion of the legs and ascends to eventually involve the

face. Fisher's variant GBS tends to involve the respiratory centers of the brainstem more quickly than typical GBS, making surveillance of respiratory status particularly important in Miller Fisher's variant GBS. The diagnosis of GBS should be especially considered in persons with histories of respiratory or gastrointestinal viral infection, immunization, or surgical procedures preceding the onset of neurologic symptoms.

3. Recurrent hemifacial sensory disturbances, particularly among older patients with a clinical history of arterial hypertension, cardiovascular disease, diabetes, and cigarette smoking, may represent a carotid artery territory transient ischemic attack (TIA). The TIA episodes are of variable duration, usually lasting <20 to 30 minutes.
4. Loss of pain sensation and thermodysesthesia with preserved light touch sensation suggest **syringobulbia,** with an expanding syrinx involving the spinal nucleus of the trigeminal nerve.
5. The rostral part of the nucleus of the spinal tract of the trigeminal nerve represents the midline facial areas, whereas the sensation fibers from the lateral facial areas terminate in the more caudal part of the nucleus at the level of the medulla and spinal cord. In acute intraparenchymal processes involving the brainstem, facial sensory loss can occur in an "onionskin" distribution with decreased sensation in the central facial areas, indicating a pontine or pontomedullary lesion. Acute presentation of **"onionskin-like" sensation deficits** in the face can accompany acute brainstem encephalitis.

C. Acute sensory loss over the scalp and neck, that is, the "top of the head." Some patients, after exposure to cold or for no obvious reason, may experience the sudden onset of lateralized discomfort or pain associated with decreased sensation in the occipital area, in the distribution of the greater or lesser occipital nerves. Acute sensory impairment in the area over the angle of the mandible, the lower part of the external ear, and the upper neck below the ear suggests neuropathy involving the great auricular nerve.

D. Acute sensory loss over half of the face, trunk, and corresponding extremities. Acute primary modality sensory loss over the entire half of the body often is a manifestation of a stroke or a traumatic CNS lesion.

1. Sensory loss in half of the body can indicate damage rostral to the upper brainstem up to the post-central gyrus and parietal area of the cerebral hemisphere contralateral to the side of the sensory deficit.
2. Acute onset of numbness, tingling, prickling, or a crawling sensation starting in the lips, fingers, or toes and spreading in seconds over half of the body may represent a partial seizure. The abnormal sensation may follow a rather stereotypical pattern, usually lasting <1 minute. The onset of focal seizures frequently reflects a focal pathologic condition such as a tumor or vascular malformation involving the contralateral hemisphere.
3. Transient hemisensory impairment can be caused by TIAs. The diagnosis of TIA is more probable if the hemisensory impairment is accompanied by motor deficits.
4. A patient with an acute vascular event in the area of the nondominant, right parietal lobe may be unable to give a reliable history because of decreased ability to appreciate motor or sensory deficits in the contralateral extremities **(anosognosia)**.
5. Hemisensory impairment manifesting as a tingling sensation, numbness, or ill-defined pain can accompany an acute vascular lesion involving the contralateral thalamus. Patients often have midline demarcation of the sensory disturbances and may be unaware of the profound sensory loss in the involved areas. Thalamic paresthesia and pain often are disabling and difficult to manage. Vascular lesions of the thalamus typically are lacunar infarcts of small thalamoperforate vessels coming off the vasculature of the circle of Willis.

E. Clinical aspects of acute sensory loss in the area of the trunk. Acute unilateral or bilateral sensory loss with a horizontal sensory level over the chest or abdomen localizes a lesion to the spinal cord and necessitates emergency evaluation to minimize residual neurologic impairment secondary to a possible spinal cord lesion.

1. **Complete transection of the spinal cord** results in bilateral weakness of legs or arms and loss of all forms of sensation one to two segments below the level of the lesion. Absence of vibration sense at the spinous process below the lesion can be helpful in localizing the spinal cord damage. A zone of increased pinprick or light touch sensation

at the upper border of the anesthetic zone may be established. Urinary and fecal incontinence is typically present.

2. Muscle weakness in a leg, with contralateral loss of pain and thermal sensation, suggests a hemispinal cord lesion on the side of the weakness, one or two segments above the sensory loss, also known as a **Brown–Séquard's syndrome.**
3. Acute loss of pain and temperature sensation can accompany **occlusion of the anterior spinal artery.** Light touch, position, and vibration senses remain intact. Anterior spinal artery syndrome can occur during aortic surgery or in advanced atherosclerotic disease of the aorta. It also can develop in the course of meningovascular syphilis or as a manifestation of collagen-vascular disease. Dissociated sensory deficits also can occur in association with acute spinal cord infarction in the "watershed" areas (T1–4 and T12–L1 levels).
4. Occasionally after falls that involve landing on the buttocks, patients may have loss of pain and temperature sensation with preserved tactile sensation one to two segments below the level of the expected spinal cord involvement. Expanding hematomas in the spinal cord gray matter compromise the ventral white commissure conducting fibers for pain and temperature sensation. Light touch and vibration senses remain intact. The dissociated sensory deficit can extend over several segments.
5. Acute ascending sensory loss for pain, soft touch, and temperature can be a manifestation of an acute spinal cord inflammatory process, that is, **acute transverse myelitis.** Decreased or absent vibration and position senses below the level of the spinal cord involvement and functional alteration in sphincters with urinary and fecal incontinence can be present. Symmetric, severe muscle weakness in the lower extremities can develop over hours. Viral diseases or vaccinations may precede the onset of neurologic symptoms by 1 to 3 weeks.
6. **Acute "saddle" sensory loss** localizes a lesion to the tip of the spinal cord at the conus medullaris. Sphincteric disturbance of bowel and bladder function often is associated.
7. Individual **nerve roots** typically are affected by trauma from spondylotic vertebral bone spurs or herniated disc protrusions.
8. The **brachial plexus** can be affected by local trauma, either during operations in the area or in accidents involving the shoulder, including birth injuries, and can become inflamed. Acute onset of tingling, numbness, and pain, usually followed in several hours or days by muscle weakness and patchy hypesthesia in the area of the shoulder girdle and proximal arm muscles, is typical of brachial plexus neuritis (neuralgic amyotrophy). Brachial plexus neuritis can occur in epidemic form. It can follow infection, vaccination, coronary bypass surgery, or parenteral administration of serum or can be idiopathic.
9. The **lumbosacral plexus** can be affected by operations in the area, including those that cause retroperitoneal hematoma. Lumbosacral plexopathy causes sensorimotor deficits and pain in the lower extremities and is commonly caused by trauma or retroperitoneal hemorrhage.
10. **Peripheral nerves** are susceptible to trauma or compression in certain classic areas.
    a. **Axillary nerve.** Dislocation of the shoulder joint, injury to the humerus, or prolonged pressure, stretching, or traction involving the arm during anesthesia or sleep can result in lesions of the axillary nerve.
    b. **Median nerve.** The median nerve can be damaged by injuries involving the arm, forearm, wrist, and hand, including stab and bullet wounds. Procedures involving needle insertion, particularly in the cubital fossa, can also result in median nerve damage manifested by sensory deficits and pain, frequently with a burning, causalgic component. In rare instances, prolonged compression during anesthesia or sleep can cause acute median nerve involvement that manifests as sensory and motor deficits. Numbness and tingling in the distribution of the median nerve that wakes a person from sleep and is relieved by shaking the hand and arm are classic signs of carpal tunnel syndrome, which typically results from repetitive motion injury around the wrist. Persons with diabetes, hypothyroidism, arthritis, or acromegaly or those who are pregnant are particularly predisposed to development of carpal tunnel syndrome.
    c. **Ulnar nerve.** Fractures and dislocations of the humerus involving the elbow, lacerating wounds, and pressure on the nerve during anesthesia, or drunkenness ("Saturday night palsy") are the most frequent causes of acute ulnar nerve damage.

d. **Radial nerve.** The radial nerve is probably the most commonly injured peripheral nerve. Injuries including dislocation and fracture of the shoulder, extended pressure on the nerve (particularly at the groove of the nerve), and fractures of the neck of the radius are the most frequent causes of radial nerve damage.
e. **Femoral nerve.** Acute femoral nerve injury may follow fractures of the pelvis and femur, dislocation of the hip, pressure or traction during hysterectomy, forceps delivery, or pressure in hematoma in the area of the iliopsoas muscle or groin. Paresthesia and sensory loss in the area of the saphenous nerve can occur as a result of injury in the area above the medial aspect of the knee in medial arthrotomy or as a complication of coronary artery bypass graft surgery.
f. **Obturator nerve.** The nerve can be damaged during surgical procedures involving the hip or pelvis, in cases of obturator hernia, or secondary to iliopsoas hematoma.
g. **Lateral femoral cutaneous nerve.** The lateral femoral cutaneous nerve can be damaged by compression by the inguinal ligament, in iliopsoas hemorrhage, or by tightly fitting garments on obese individuals, causing tingling, numbness, and pain, that is, meralgia paresthetica.
h. **Sciatic nerve.** Acute sciatic nerve damage can occur in association with fractures or dislocations of the hip, hip joint surgery, other pathologic conditions of the pelvis including gunshot wounds or injections in the vicinity of the sciatic nerve.
i. **Peroneal nerve.** Most peroneal nerve lesions are traumatic, including those caused by compression exerted at the upper and outer aspects of the leg, stretching of the hip and knee, or surgical procedures involving the knee joint.
j. **Tibial nerve.** The tibial nerve is injured mostly in the popliteal fossa at the level of the ankle or foot. Injury at the tarsal tunnel where the nerve crosses the medial malleolus causes sensory loss in the toes and dorsum of the foot.

IV. ETIOLOGY OF ACUTE SENSORY LOSS

A. Infectious–parainfectious neurologic diseases are preceded by or associated with acute febrile diseases involving the upper respiratory or gastrointestinal system or the lower urinary tract. Parainfectious involvement of the CNS or peripheral nervous system (PNS) typically follows the onset of clinical symptoms of the infectious process by 1 to 3 weeks.
B. Inflammatory-demyelinating disease can be parainfectious or postinfectious but can also be idiopathic or autoimmune.
C. Ischemic–hemorrhagic neurologic disorders manifesting as acute CNS or PNS involvement usually occur among older persons with vascular risk factors.
D. Traumatic–compressive lesions of the CNS and PNS can manifest as acute sensory loss. Complications of surgical procedures, venipuncture, or intravascular injection can cause acute sensory loss, usually secondary to peripheral nerve damage.

V. DIAGNOSTIC APPROACHES TO ACUTE SENSORY LOSS

Diagnostic approaches to acute sensory loss are focused by the localization of the lesion (Sections I, II and III) and by suspected etiologic factor (Section IV).

A. PNS evaluation. If a lesion localizes to a particular peripheral nerve, the extremity and nerve can be evaluated radiographically and electrophysiologically.
1. Radiographs of the involved limb can help identify fractures or bony deformities that can cause focal compression of damage to the nerve. CT or MRI of the brachial or lumbosacral plexus can be useful in identifying the nature of damage.
2. **EMG with nerve conduction velocity studies (NCVs)** can be helpful in documenting and localizing damage to a peripheral nerve, a plexus, or a nerve root and in providing prognostic information (see Chapter 33). In a traumatized nerve or root, abnormalities may not appear immediately on nerve conduction studies. It also takes approximately

2 weeks for denervative change to occur in muscles innervated by damaged nerves, so an initially unremarkable or borderline EMG must be repeated if there is continued suspicion of damage. In the acute period, a demyelinated nerve can show slowing of nerve conduction, conduction block across demyelinated nerve segments, and slowing of F waves that reflect proximal nerve root damage. The greater the denervation and axonal dropout found at subacute EMG/NCV studies, the worse the prognosis.

B. Spinal cord evaluation. Localization of a lesion to the spinal cord necessitates neuroimaging of the cord. Traumatic lesions necessitate immediate imaging of an immediately stabilized spine by means of traditional radiographs and subsequent imaging of the spinal cord parenchyma by means of MRI or CT myelography.

1. **MRI** is the preferred technique for imaging the spinal cord parenchyma, and use of gadolinium can be helpful in identifying acute inflammatory lesions or syringomyelic cavities.
2. **CT myelography** can be used to examine segments of the cord and is especially good at depicting bone, disc, and ligamentous structures that may impinge on the spinal cord.
3. **Somatosensory-evoked responses** can help determine whether there is slowed conduction of somatosensory stimuli from arms or legs in the somatosensory pathways from spinal cord to cortex and can crudely localize the lesion.
4. **MR angiography** can occasionally noninvasively help identify a suspected vascular lesion in the spinal cord, but traditional angiography of spinal vessels is the gold standard to identify lesions.

C. Brain evaluation. Acute sensory loss that localizes to the brain, including cerebral cortex or brainstem, can be evaluated by several techniques.

1. Traditional **radiographs,** including sinus radiographs, can be helpful.
2. **MRI** can most precisely localize a lesion and can include MR angiography and MR venography to examine blood vessels. Diffusion-weighted imaging has very high specificity in acute stroke (see Chapter 32). For suspected inflammatory-demyelinating or postinfectious processes, MRI is the procedure of choice. Gadolinium contrast material should be administered to assess whether there is acute enhancement, which suggests active inflammation and breakdown of the blood–brain barrier. The presence of subclinical white matter lesions on MRI brain during a clinically isolated bout of transverse myelitis indicates increased risk of development of multiple sclerosis.
3. **Cerebral angiography** may be necessary to diagnose vascular abnormalities such as ruptured aneurysm, atherosclerotic narrowing, vasculitis, and sinus thrombosis.
4. **Electroencephalography** can aid in the diagnosis of seizures (see Chapter 33).

D. Blood work can be used to diagnose infectious or inflammatory conditions that can cause acute sensory loss, including complete blood cell count, blood cultures when indicated, erythrocyte sedimentation rate, antinuclear antibodies, rheumatoid factor, angiotensin-converting enzyme level, rapid plasma reagent test, Lyme's titer, antineutrophil cytoplasm autoantibodies, glucose level, and hemoglobin A_{Ic}. Suspected vascular–hemhorragic processes should be assessed for hypercholesterolemia and hypercoagulable or prothrombotic states.

E. Examination of CSF can show whether there is acute protein elevation, glucose depression, or WBC elevation suggestive of infectious or inflammatory causes of for acute sensory loss (see Chapter 33). Hypoglycorrhachia can indicate the need for further attempts to isolate certain infectious agents such as fungi or acid-fast bacilli. The nature of CSF pleocytosis can dictate further evaluation; the most typical inflammatory causes of postinfectious sensory loss cause lymphocytic pleocytosis. To further pursue postinfectious and demyelinating etiologic factors, spinal fluid should be examined for IgG level and IgG index, both of which are elevated in multiple sclerosis and often in transverse myelitis, and for the presence of oligoclonal IgG bands in CSF but not serum. These bands are present in most cases of multiple sclerosis and in many forms of parainfectious or postinfectious encephalomyelitis. Myelin basic protein levels in CSF can indicate ongoing demyelination. For suspected infectious causes, cultures and smears for bacteria, acid-fast bacilli, and fungus are important. Serologic and PCR tests also can be done for many viruses, including herpes simplex types 1 and 2, Epstein–Barr

virus, cytomegalovirus, human herpesvirus type 6. A CSF VDRL test and angiotensin-converting enzyme level are useful.

VI. REFERRALS

Cases of acute sensory loss should be referred to a neurologist if:

A. Sudden onset or resolution suggests TIAs.

B. Radiculopathy is suspected and focal neurologic deficits are present (weakness and reflex loss).

C. Fever is present, and there is a suspicion of encephalitis or cortical sinus thrombosis.

D. Deficits worsen, ascend, or evolve to include motor signs and symptoms, suggesting GBS.

E. Acute deficit localizes to the spinal cord. A neurosurgeon also should be informed.

Recommended Readings

Biller J, Gruener G, Brazis PW. *DeMyer's The Neurologic Examination: A Programmed Text*. 6th ed. New York, NY: McGraw-Hill; 2011.

Brazis PW, Masdeu JC, Biller J. *Localization in Clinical Neurology*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins, Wolters Kluwer; 2011.

Fisher CM. Pure sensory stroke and allied conditions. *Stroke*. 1982;13:434–447.

Kimura J. *Electrodiagnosis in Diseases of Nerve and Muscle*. Philadelphia, PA: FA Davis Co; 1984.

Koski CL. Guillain Barré syndrome and chronic inflammatory demyelinating polyneuropathy: pathogenesis and treatment. *Semin Neurol*. 1994;14:123–130.

Patten J. *Neurological Differential Diagnosis*. New York, NY: Springer-Verlag; 1980.

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69:292–302.

Scott TF, Bhagavatula K, Snyder PJ, et al. Transverse myelitis: comparison with spinal cord presentations of multiple sclerosis. *Neurology*. 1998;50:429–433.

CHAPTER

28 Approach to the Hyperkinetic Patient

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Hyperkinetic movement disorders are abnormal involuntary movements characterized by excessive movement. It may be classified as tremor, dystonia, chorea, myoclonus, and tics (Table 28.1).

According to etiology, hyperkinetic movements may be classified as follows:

1. Hereditary.
2. Nonhereditary primary hyperkinetic movement disorders.
3. Degenerative.
4. Secondary: ischemic or posthypoxic, demyelinating, tumoral, post-traumatic, inflammatory, infectious, immunologic, endocrinologic, or metabolic.
5. Drug-induced.

I. TREMOR

A. Definition. Tremor is a rhythmic, involuntary back-and-forth oscillation of part of the body. It is described clinically by the location where it develops (hands, feet, back, neck, face, and voice), and the situations, postures, or movements that trigger or enhance it (action, at rest, and maintenance of a posture), and electrophysiologically by the frequency, amplitude, and pattern of muscle activation, as assessed by accelerometry and surface electromyography.

B. Phenomenologic classification.

1. **Rest tremor**. Tremor that occurs in a body part that is not voluntarily activated and is completely supported against gravity. Rest tremor amplitude always diminishes during target-directed movements, which helps to separate rest tremor from postural tremors that continue when the limb is supported. It increases with mental stress (counting backwards), or when movements of another body part are performed (especially walking). It is mostly found in Parkinson's disease (PD), but also in other parkinsonian syndromes, including drug-induced parkinsonism. Its presence indicates dysfunction of the nigrostriatal dopamine pathway or its efferent projections to basal ganglia-thalamo-cortical circuits.
2. **Action tremor**. Any tremor that is produced by voluntary contraction of muscle, and it includes postural, simple kinetic, intention tremor, and task-specific kinetic tremor.
   a. **Postural tremor**. Tremor that is present while voluntarily maintaining a position against gravity. It is usually documented by having the patient outstretch the arms.
   b. **Simple-kinetic tremor.** Tremor that occurs during voluntary action that is not target-directed.
   c. **Intention tremor**. Action tremor whose amplitude increases substantially during the pursuit of a target or goal. Its presence suggests a disturbance of the cerebellum or its afferent/efferent pathways.
   d. **Task-specific kinetic tremor.** Tremor that occurs during specific activities such as the primary writing tremor and occupational tremors. These tremors are often associated with dystonia.

C. Etiologic classification.

1. Physiologic and enhanced physiologic.
2. Hereditary (familial, fragile X-associated tremor/ataxia syndrome [FXTAS], Wilson's disease, spinocerebellar ataxias [SCAs], hereditary hemochromatosis, and acute intermittent porphyria).
3. Nonhereditary primary tremor: essential and orthostatic.

TABLE 28.1 Hyperkinetic Movement Disorders

Term	Clinical Manifestations
Tremor	Rhythmic oscillation of agonist and antagonist muscles
Dystonia	Sustained and patterned involuntary muscular spasms, usually with a twisting component, producing abnormal postures or positions
Chorea	Irregular, rapid, and continuous flow of random muscle contractions from one part of the body to another
Ballismus	Violent flinging movements of the limbs, usually affecting only one side of the body (hemiballismus)
Myoclonus	Sudden, lightning-like, and jerky involuntary movements caused by muscular contractions or inhibitions
Tics	Repeated and stereotyped movements or sounds that are preceded by an urge or sensation in the affected muscle group, and a sense of temporary relief once the movement is made

4. Degenerative: PD and other parkinsonisms.
5. Ischemic and posthypoxic.
6. Demyelinating disease.
7. Inflammatory, infectious or immunologic: AIDS and brain abscesses.
8. Neuropathic.
9. Endocrinologic/metabolic: thyroid and hypoglycemia.
10. Post-traumatic.
11. Drug-induced or toxic: valproate acid, amlodipine, selective serotonin reuptake inhibitors (SSRIs), prednisone, cyclosporine A, and tacrolimus **(also see tardive syndromes).**

D. Pathophysiology. Tremor is not associated with any uniform brain lesion or clear histopathologic changes in the brain. However, two regions within the central motor pathways, the inferior olive and the relay nuclei of the thalamus, demonstrate oscillatory behavior, and their pharmacologic manipulation in the harmaline mouse model may produce or improve tremor. These regions are functionally interconnected with the cerebellum. Thus, the inferior olive, relay nuclei of the thalamus, and the cerebellum are the principal candidates for the origin of any pathologic central tremor.

E. Selected clinical syndromes.

1. **Physiologic tremor** is a low-amplitude and high-frequency (8 to 12 Hz) postural tremor that is most prominent in outstretched hands. It can be present in normal subjects but can be enhanced under certain circumstances, including fever, drugs, excited mental states, alcohol withdrawal, and caffeine use.
   a. **Differential diagnosis.**
      (1) Metabolic or endocrine derangements.
      (2) Essential tremor.
      (3) Cortical myoclonus.
      (4) Drug-induced or withdrawal.
      (5) Anxiety.
   b. **Evaluation.**
      (1) Blood tests to rule out metabolic problems: hyperthyroidism, hypercorticism, hyperparathyroidism, hypocalcemia, hepatic encephalopathy, hypoglycemia, and pheochromocytoma.
      (2) Review of medications (most common cause): thyroid drugs, corticosteroids, lithium, theophylline, β_2-adrenergic receptor agonist, SSRIs, and sodium valproate.
      (3) Assessment for anxiety.
2. **Essential tremor** is the most frequent neurologic disease causing tremor in the general population. It is an action tremor, mainly postural and kinetic. It is bilateral, largely symmetric, but it can be also asymmetric or even unilateral. The frequency usually is 4 to 12 Hz but may decrease with age. Conversely, amplitude increases during the

follow-up. Its major clinical feature is postural tremor of the hands, but it also can be present in other body parts (distal legs, voice, and head). About 5% of patients may present with tremor almost exclusively in the head and voice. Improvement of tremor amplitude with alcohol is a characteristic feature of the disease but is not present for most patients.

Although most patients have strong family histories, and three gene loci (ETM1 on 3q13, ETM2 on 2p24.1, and a locus on 6p23) have been identified in patients and families with the disorder, the cause of essential tremor is unclear. In recent years, systematic postmortem studies have shown essential tremor to be associated with clearly identifiable structural changes, including Purkinje's cell loss, development of torpedoes in the cerebellum and, in some patients, deposition of Lewy's bodies in the brainstem.

a. **Differential diagnosis.**
   (1) Physiologic tremor **(see above)**.
   (2) Metabolic or endocrine derangements.
   (3) Wilson's disease (when age of onset of essential tremor is under 40 years).
   (4) Rhythmic myoclonus and cortical tremor.

b. **Evaluation.**
   (1) Review medication and blood tests to rule out metabolic problems (**see physiologic tremor**).
   (2) Assess history of caffeine use, smoking, or alcohol withdrawal.
   (3) Evaluate serum ceruloplasmin to rule out Wilson's disease (under 40 years).

3. **PD** is the most frequent cause of rest tremor. It is typically defined by bradykinesia, rigidity, and impairment of postural reflexes. The neural correlates of rest tremor in PD are unknown, and the participation of other neurotransmitter systems apart from the dopaminergic dysfunction is likely. **Parkinsonian tremor** occurs at 3 to 7 Hz. It may be unilateral in the early stages of the disease, but it soon spreads to the contralateral side. Characteristically, it remains asymmetric through the course of the disease. Mental stress or movements of another body part (contralateral hand and gait) typically trigger the rest tremor or increase tremor amplitude. Parkinsonian tremor can be also present while maintaining a posture. Postural tremor in PD has been designated as a reemergent tremor, with a latency for the tremor to appear about 9 seconds, which is significantly longer than the latency observed in patients with essential tremor (1 to 2 seconds).

   a. **Differential diagnosis.**
      (1) Other parkinsonian syndromes: multisystem atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), dementia with Lewy's bodies (DLB), Alzheimer's disease (AD) with extrapyramidal features, and frontotemporal dementia with parkinsonism.
      (2) SCA (SCA2, SCA3, SCA8, and SCA12).
      (3) Vascular parkinsonism.
      (4) Drug-induced parkinsonism.
      (5) Structural lesions involving the substantia nigra pars compacta.

   b. **Evaluation.**
      (1) Review of drugs: dopamine receptor blocking drugs (haloperidol, risperidone, olanzapine, and metoclopramide), calcium channel blockers, and trimetazidine.
      (2) CT scan or brain MRI to rule structural lesions involving the substantia nigra, basal ganglia, or diffuse cerebral white matter disease.
      (3) Transcranial ultrasonography can show distinctive patterns in PD versus MSA, PSP, or CBD.
      (4) Dopamine transporter SPECT, a marker of the integrity of the presynaptic nigrostriatal pathway, is increasingly used to separate PD from vascular parkinsonism, essential tremor, or psychogenic parkinsonism.

4. **Cerebellar tremor** is clinically defined by pure or dominant intention tremor. It may be uni- or bilateral. Postural tremor may be present, but no rest tremor. Typically, tremor frequency is below 5 Hz. Cerebellar tremor is often associated with dysmetria (finger-to-nose and heel-to-shin testing maneuvers) and hypotonia. This kind of tremor can be considered a symptomatic tremor produced by any disease that affects the functionality of the cerebellum or its afferent/efferent pathways.

a. **Differential diagnosis.**
   (1) Alcohol or drug abuse.
   (2) Drug-induced.
   (3) Multiple sclerosis.
   (4) SCA, autosomal recessive hereditary ataxias, and FXTAS.
   (5) Space-occupying mass, or an ischemic, toxic, or infectious disorder in the brainstem, the cerebellum, or the frontal lobes (due to diaschisis).

b. **Evaluation.**
   (1) Brain MRI to rule out structural lesions in the posterior fossa or the frontal lobes.
   (2) Review of drugs: phenytoin, carbamazepine, and phenobarbital.

5. **Holmes' tremor** is clinically defined by rest and intention tremor, with postural tremor present in many patients. It is mostly unilateral. Postural tremor tends to be more severe than tremor at rest, and intention tremor more severe than the postural tremor. Tremor frequency is usually <4.5 Hz. This is also a symptomatic tremor that occurs after a brainstem, midbrain, or thalamic lesion, when two systems, the dopaminergic nigrostriatal system and the cerebellothalamic system, are lesioned. A variable delay (4 weeks to 2 years) between the lesion and the appearance of the tremor is typical.

   Differential diagnosis and evaluation (see cerebellar tremor).

   Treatment. Holmes' tremor and thalamic tremor do not usually respond to pharmacologic treatments. Although the effects of thalamic deep brain stimulation in the ventral intermediate nucleus are incomplete, functional surgery in complex tremor syndromes appears as the only available therapeutic option and provides significant and lasting functional improvement.

6. **FXTAS.** Over the past decade, it has been shown that premutation carriers (especially males) of the FMR1 mutation (55 to 200 CGG repeats) are at risk of developing the FXTAS. Core clinical features of FXTAS are progressive cerebellar gait ataxia, mild parkinsonism, autonomic dysfunction, peripheral neuropathy, and intention tremor. Postural and rest tremor may be also present. FXTAS is often misdiagnosed as essential tremor and PD. As the diagnosis of FXTAS has substantial implications regarding genetic counseling, it is important to consider FXTAS as a cause of tremor when ataxic symptoms are also present.

   a. Differential diagnosis.
      (1) Essential tremor.
      (2) PD.
      (3) Atypical parkinsonian disorders (MSA, PSP, and CBD).
      (4) SCAs and other hereditary ataxic syndromes.
      (5) DLB.

   b. **Evaluation.**
      (1) The presence of combined essential-like tremor, along with gait ataxia or parkinsonism in an adult (usually male) with a grandchild with intellectual disability, should prompt genetic testing for FXTAS.

II. DYSTONIA

A. **Definition.** Dystonia is a syndrome characterized by excessive, patterned, intermittent or sustained, and sometimes painful muscle spasms that produce abnormal postures or repetitive movements. Dystonic contractions are mainly characterized by the following:

1. Consistent directionality: The movements are patterned and repeatedly involve the same muscle groups.
2. Aggravation by voluntary movement (action exacerbation). Dystonia may be also triggered by particular actions such as writing or playing a musical instrument (task-specific dystonia).
3. Presence of a "sensory trick," the use of a tactile or proprioceptive stimulus, generally in some particular spot in the same area where the dystonic movements are present, which can improve the muscle contractions.

B. Phenomenologic classification

1. Focal. The abnormal movements affect single body region such as cervical dystonia, blepharospasm, spasmodic dysphonia, oromandibular dystonia, or brachial dystonia.
2. Segmental. The abnormal movements affect two or more contiguous body parts, as in Meige's syndrome (blepharospasm plus oromandibular dystonia), craniocervical dystonia, or bibrachial dystonia.
3. Multifocal. Two or more noncontiguous body areas are involved.
4. Hemidystonia. The abnormal movements affect one side of the body.
5. Generalized. Abnormal movements are present in the legs (or in one leg and the trunk) plus at least one other area of the body.

C. Classification by age of onset.

1. Early-onset: ≤26 years.
2. Late-onset: >26 years.

D. Etiologic classification.

1. Primary, or idiopathic, dystonia.
   a. Primary torsion dystonia (PTD). DYT 1 (Oppenheim's dystonia), DYT2, DYT4, DYT6, DYT7, and DYT 13.
2. Secondary dystonia.
   a. Dystonia-plus syndromes. Dystonic syndromes with other neurologic features in addition to dystonia, in which clinical and laboratory findings suggest neurochemical disorders, with no evidence of neurodegeneration.
      (1) Dopa-responsive dystonias (DRD).
         (a) Segawa's disease (DYT5) = GTP cyclohydrolase 1 deficiency.
         (b) Tyrosine hydroxylase deficiency, other biopterin deficiencies, and dopamine-agonist-responsive dystonia due to deficiency of aromatic L-amino acid decarboxylase.
      (2) Myoclonus-dystonia (DYT11).
      (3) Rapid-onset dystonia-parkinsonism (DYT12).
   b. Associated with heredodegenerative. Neurodegenerative diseases in which dystonia is sometimes a prominent feature.
      (1) Huntington's disease, pantothenate kinase-associated neurodegeneration (PKAN—formerly known as Hallervorden–Spatz's disease), neuroacanthocytosis, SCA, dentatorubropallidoluysian atrophy, and mitochondrial diseases associated with parkinsonian disorders (PD, CBD, PSP, and MSA).
   c. Acquired dystonia. When dystonic movements are symptomatic of an exogenous or environmental cause.
      (1) Main causes. Cerebrovascular diseases, CNS tumor, central trauma, infectious or postinfectious encephalopathies, toxins (CO and manganese), metabolic diseases (Wilson's disease and GM1 gangliosidosis), paraneoplastic syndromes, perinatal anoxia, kernicterus, and peripheral trauma.

C. Pathophysiology. Dystonia is attributed to basal ganglia abnormalities and to a dysfunction of the cortico-striatothalamo-cortical circuits. Idiopathic dystonia is not associated with any particular structural brain lesion. However, neurophysiologic and neuroimaging techniques have shown a correlation between the co-contraction and overflow of EMG activity of inappropriate muscles, with reduced pallidal inhibition of the thalamus due to lower firing rates, large sensory receptive fields, and irregular discharges in bursts or groups of bursts in neurons of the medial globus pallidus. Supporting the theory of basal ganglia dysfunction, secondary dystonia is mostly observed in patients with lesions of the putamen and connections with the thalamus and cortex.

D. Selected clinical syndromes.

1. **PTD.** It refers to those syndromes in which dystonia is the only phenotypic manifestation (except for tremor). In cases of PTD, there is no history of brain injury, no laboratory findings exclusive of genetic tests to suggest a cause for dystonia, no consistent associated brain pathology, and no improvement with a trial of low-dose levodopa. Some of these cases can be attributed to a genetic cause. **Early-onset PTD (Oppenheim's dystonia)** is inherited as an autosomal dominant trait with reduced penetrance (30% to 40%). The genetic mutation for the most frequent and severe form of early-onset PTD, named DYT1, was mapped to chromosome 9q34, which encodes

the protein TORSIN, whose function remains unknown. The disorder develops before 26 years of age in nearly all cases. It normally begins in one arm or a leg, and spreads to other limbs and trunk, leading to the most severe generalized form of the disease in most cases. Selective or pronounced craniocervical or orofacial involvement is unusual. Conversely, late-onset PTD (>26 years—DYT4, DYT6) normally involves the upper part of the body (cranial–cervical region) and usually remains focal or segmental. In spite of this archetypical pattern, dystonia may remain localized as writer's cramp in some patients with early-onset PTD.

a. **Differential diagnosis.**
   (1) Perinatal hypoxia.
   (2) Head trauma.
   (3) DRD.
   (4) Wilson's disease.
   (5) PKAN and neuroferritinopathy.
   (6) Other metabolic disorders. Glutaric acidemia type 1, GM1 and GM2 gangliosidosis, metachromatic leukodystrophy, sialidosis, Krabbe's disease, Niemann–Pick's type C, vanishing white matter disease, and biotinidase deficiency.
   (7) Huntington's disease (Westphal's variant).
   (8) Ataxia-telangiectasia.
   (9) Leigh's syndrome.

b. **Evaluation.**
   (1) Brain MRI.
      (a) Primary dystonia usually has normal MRI.
      (b) "Eye of the tiger" sign (globus pallidus central hyperintensity with surrounding hypointensity on T2-weighted images) is due to iron deposition in the globus pallidus and very suggestive of PKAN.
      (c) Wilson's disease has also distinctive neuroimaging findings, with T2-weighted globus pallidal hypointensity, T2-weighted "face of giant panda" sign (hyperintensity of the midbrain, hypointensity of the aqueduct, and relative sparing of red nucleus, superior colliculus, and substantia nigra pars reticulata), and T1-weighted striatal hyperintensity (bilateral thalamus and lenticular nucleus).
   (2) Patients with onset before 26 years of age should be always considered for trial of low-dose levodopa, to exclude DRD.
   (3) Wilson's disease. To exclude this disorder, slit-lamp eye examination for Kayser–Fleischer's rings and determination of serum ceruloplasmin level should be performed in dystonia patients younger than 50 years.
   (4) Screening of metabolic inherited diseases, when atypical features of DYT1 are present (bulbar and orofacial symptoms, cognitive impairment, behavioral disturbances, and polyneuropathy).
   (5) Patients with onset before 26 years of age should be considered for genetic testing for the DYT1 gene. A detailed family history should be obtained.

2. **Focal dystonia.**
   - **Blepharospasm** is a disorder that consists of uncontrollable involuntary spasms of the eyelids causing spontaneous closure. It often interferes with vision, resulting in functional blindness. It may be worsened by bright light or stress.
   - **Oromandibular dystonia** consists of grimacing of the lower part of the face, usually involving the mouth, jaw, and platysma muscle. Depending on the nature of the oromandibular movements, jawclosing, jaw opening, and jaw deviation oromandibular dystonias are differentiated.
   - **Cervical dystonia** or spasmodic torticollis consists of intermittent uncontrollable spasms of the neck muscles. The neck may involuntarily turn, tilt, or rotate forward, sideways, or backward.
   - **Spasmodic dysphonia** involves only the vocal cords. There are two types of spasmodic dysphonia. With **adductor-type** spasmodic dysphonia, hyperadduction of the cords produces an intermittent strain and strangle quality to the voice. Often patients also report tightness in the throat during the spasms. With the rarer **abductor type** of spasmodic dysphonia, there is a whispering quality to the voice.

- **Task-specific dystonia.** The dystonic movements are brought out by performing a specific task such as writing, typing, or playing a musical instrument. Writer's cramp is the most common and most underdiagnosed form of limb dystonia. Examples of task-specific dystonia include a secretary who has dystonic hand cramps only while typing, and a violinist who has finger spasms only while playing.

a. **Differential diagnosis of focal dystonia.**
   (1) Drug-induced (most common cause of secondary focal dystonia).
   (2) Pseudodystonias.
      (a) Sandiffer's syndrome. Torticollis and paroxysmal dystonic postures induced by gastroesophageal reflux.
      (b) Posterior fossa tumors.
      (c) Chiari's malformation.
      (d) Atlantoaxial subluxation.
   (3) Structural lesions involving the basal ganglia, thalamus, brainstem, or the cervical spinal cord (ischemic, demyelinating, inflammatory, infectious, immunologic lesion, and space-occupying mass).

b. **Evaluation.**
   (1) Review of medication record for dopamine receptor blocking drugs (metoclopramide, clebopride, haloperidol, risperidone, and tiapride), flupenthixol, melitracene, anti-dizziness drugs (tietilperazine, sulpiride, and veralipride).
   (2) MRI of the brain including the posterior fossa and the cervical spinal cord. To rule out structural lesions, or images suggestive of metabolic inherited disorders, or of neurodegeneration with brain iron accumulation (PKAN and neuroferritinopathy).

3. **Acquired dystonia.** These disorders relate usually to lesions in the CNS, mostly in the basal ganglia, although peripheral trauma in the neck or limbs can result in dystonic posturing of that body part. Stroke, CNS tumor or demyelinating disease, perinatal anoxia, and trauma are the most frequent causes of acquired dystonia. Acquired dystonia typically involves one side of the body (hemidystonia) or only one extremity and may be accompanied by impairment of different neural systems: weakness, sensory disturbances, or pyramidal signs. Peripherally induced dystonia may show atypical dystonic features, such as fixed postures and maintenance of dystonia during sleep, and a worse response to botulinum toxin than seen with other acquired forms.
   a. **Evaluation.** MRI of the brain including the posterior fossa and the cervical spinal cord to rule out structural lesions.
4. **Wilson's disease.** It is the most common known metabolic defect causing secondary dystonia. It is an inherited deficit in copper metabolism.
   a. Neurologic symptoms affecting the basal ganglia, including bradykinesia, dysarthria, dystonia, tremor, ataxia, and abnormal gait, occur in 40% to 60% of patients. Spasmodic dysphonia is a common feature.
   b. Wing-beating tremor is classically described in patients with Wilson's disease (55%). This tremor is absent at rest and develops after the arms are extended. Rest tremor may also be present in 5% of the patients.
   c. Psychiatric symptoms (65%) (psychosis, depression, irritability, agitation, and disinhibition), mild cognitive impairment (70%), and dementia (5%) can be associated with the motor manifestations.

      Early treatment can reverse the liver involvement in Wilson's disease and stop the neurologic impairment.

   Differential diagnosis and evaluation (see PTD).
5. **DRD—DYT5**. This childhood onset disease usually begins with leg dystonia that gradually progresses to other parts of the body. Typical features are a diurnal fluctuation of the symptoms, so that they worsen as the day progresses or after intense exercise, and they improve after sleep. Patients may also show extensor plantar responses with hyperreflexia in the lower limbs, tremor, and parkinsonism. The most characteristic feature of DRD is a dramatic and sustained response to low-dose levodopa, without the typical complications of motor fluctuations and dyskinesias.
6. **Myoclonus-dystonia (DYT11)**. This disorder is characterized by involuntary jerks and dystonic movements and postures, both of which may be dramatically alleviated with alcohol. It normally begins in the first or second decade of life (5 to 18 years), with

myoclonic jerks and dystonic movements most frequently involving the arms, neck, and face. Although spread to axial muscles and the legs is typical, the condition is compatible with an active life of normal span. Obsessive-compulsive disorder, anxiety/panic/phobic disorders, and alcohol dependence are frequently associated with the motor manifestations.

7. **Rapid-onset dystonia-parkinsonism (DYT12)**. This very rare condition involves dystonic spasms, bradykinesia, postural instability, severe dysarthria, and dysphagia that develop abruptly over a period ranging from several hours to weeks. Some patients report specific triggers consisting of either physical or psychological stress. There is little response to dopaminergic drugs, and the neurologic sequelae remain stable over time.
8. Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis. Encephalitis due to NMDA receptor antibodies has been recently associated with the development of jaw opening and other orofacial dystonias. Distonic movements have been reported in combination with opisthotonic posturing, seizures, psychosis, and other behavioral changes. Anti-NMDA receptor antibodies have been even found to cause isolated hemidystonia. As NMDA receptors are present in the neuronal membrane, discovery and treatment of neoplasias producing anti-NMDA receptor antibodies (ovarian and mediastinic teratoma, breast cancer, and pancreatic cancer), and immunotherapy can improve and even resolve the neurologic condition.

III. CHOREA

A. Definition. Chorea is characterized by arrhythmic involuntary movements resulting from a continuous flow of random muscle contractions. When choreic movements are more severe, assuming a large amplitude and sometimes violent character, they are called ballism. Although typical choreic movements are predominantly distal, ballistic movements are more proximal. Athetosis is a related writhing and twisting movement that manifests predominantly in distal arms. Regardless of its cause, chorea has very distinctive clinical features. The differential diagnosis of choreic syndromes relies on differences in the presence of other accompanying findings.

B. Etiologic classification.

1. **Genetic choreas.**
   a. Huntington's disease.
   b. Huntington's disease-like 2 (HDL2) and other HD-like symptoms.
   c. Neuroacanthocytosis.
   d. PKAN.
   e. Ataxia telangiectasia.
   f. SCA, types 2, 3, or 17.
   g. Dentatorubropallidolyusian atrophy.
   h. Benign hereditary chorea.
   i. Paroxysmal kinesigenic choreoathetosis.
2. **Structural basal-ganglia lesions.**
   a. Vascular chorea in stroke.
   b. Hemodynamic ischemia secondary to carotid stenosis.
   c. Mass lesions (lymphoma and metastatic brain tumors).
   d. Multiple sclerosis plaques.
   e. Extrapontine myelinolysis.
   f. Polycythemia vera (generally not related to focal vascular lesions in the basal ganglia).
   g. Moyamoya disease.
   h. Post-pump chorea (generalized chorea immediately after extracorporeal circulation. Benign prognosis with spontaneous remission in most cases.)
3. **Parainfectious and autoimmune disorders.**
   a. Sydenham's chorea.
   b. Systemic lupus erithematosus (SLE).
   c. Chorea gravidarum (chorea during pregnancy).
   d. Antiphospholipid antibody syndrome.
   e. Behçet's disease.

f. Postinfectious or postvaccinal encephalitis.
g. Paraneoplastic choreas (anti-CV2/CRMP5 or anti-Hu antibodies, associated with small cell lung cancer, Hodgkin's lymphoma, or thymoma).

4. **Infectious chorea.** HIV primoinfection, toxoplasmosis, cysticercosis, diphtheria, infective endocarditis, neurosyphilis, viral encephalopaties (mumps, measles, and varicella), herpes simplex, and parvovirus B19.
5. **Metabolic or toxic encephalopathies.**
   a. Hyperglycemic-induced hemichorea–hemiballismus.
   b. Acute intermittent porphyria.
   c. Hyponatremia/hypernatremia.
   d. Hyperthyroidism.
   e. Hypoparathyroidism.
   f. Hepatic/renal failure.
   g. CO, manganese, mercury, and organophophorate intoxication.
   h. Hyperhomocysteinemia±vitamin B_{12} deficiency.
6. **Drug-induced chorea.**
   a. Antiparkinsonian drugs. L-Dopa and dopamine agonists.
   b. Dopamine receptor blocking agents (chronic exposure).
   c. Antiepileptic drugs. Phenytoin, carbamazepine, valproic acid, and gabapentin.
   d. Psychostimulants and other drugs. Amphetamines, cocaine, heroin, and methylphenidate.
   e. Methadone.
   f. Calcium-channel blockers. Cinnarizine, flunarizine, and verapamil.
   g. Oral contraceptives (likely to induce chorea in patients with previous choreic episodes—such as SLE or Sydenham's chorea).
   h. Steroids.
   i. Antihistamine drugs.
   j. Others. Lithium, baclofen, digoxin, tryciclic antidepressants, cyclosporine, theophylline, ribavirine, and α-interferon.

C. Pathophysiology. Chorea results from facilitation of the striato-pallido-thalamic output pathway, leading to thalamo-cortical disinhibition of previously learned and patterned movements. This failure of control comes from dysfunction of neural networks in the basal ganglia that are interconnected with the motor cortical areas. Neurophysiologic and lesional studies and cases of chorea in patients with focal lesions in the basal ganglia have shown that failure of inhibition of movements relates mainly to dysfunction of the caudate nucleus and the subthalamic nucleus.

D. Selected clinical syndromes.

1. **Huntington's disease** is an autosomal-dominant progressive neurodegenerative disease characterized by chorea, dystonia, loss of balance, cognitive decline, and behavioral changes. Neurodegeneration primarily affects the head of the caudate nucleus and the frontal cortex. The genetic disorder is caused by a trinucleotide (CAG) repeat expansion in the gene encoding huntingtin on chromosome 4p16.3. Polyglutamine expansions are the main component of Huntington that lead to neuronal degeneration, a pattern also seen in several SCA. Healthy individuals have fewer than 35 CAG repeats, and repeats of 40 or above cause Huntington's disease with 100% penetrance. Individuals with 36 to 39 repeats can develop the disease, but penetrance is incomplete.

   The mean age at onset is 40 years. Although chorea is the main feature of the disease, the full spectrum of motor impairment includes eye-movement abnormalities, parkinsonism, dystonia, myoclonus, tics, cerebellar ataxia, spasticity with hyperreflexia, dysarthria, and dysphagia. Features of chorea are very variable, but choreic orofacial movements and mild slow, sinusoidal, and flowing distal movements in the four extremities are very common in the early stages of the disease. With progressing illness, dystonia and parkinsonism may become the main motor features. Behavioral and cognitive impairment affect almost all patients, with depression, anxiety, apathy, irritability, agitation, obsessive-compulsive symptoms, and social disinhibition accounting for the most frequent disorders. Young onset disease (<20 years, so-called Westphal's variant) is associated with >55 CAG repeats and is characterized by predominant dystonic symptoms, myoclonus, parkinsonism, and seizures.

2. **Sydenham's chorea.** It is the most common cause of acute chorea in children worldwide. It has a female preponderance, and the typical age of onset is 8 to 9 years. Sydenham's chorea represents the prototype of chorea resulting from immune mechanisms, related to rheumatic fever. Up to 25% of patients with rheumatic fever develop generalized chorea 4 to 8 weeks after an episode of ß-haemolytic streptococcal pharyngitis, although it can be manifested as hemichorea in 20% of patients. Molecular similarities between streptococcal and basal ganglia antigens seem to be the main pathogenetic mechanism leading to chorea.

   Chorea is frequently accompanied by hypotonia, tics, motor impersistence, and behavioral abnormalities (ADHD and obsessive-compulsive symptoms). Mitral valvulopathy is also present in up to 60% to 80%. Sydenham's chorea has a good prognosis. Spontaneous remission often occurs after 8 to 9 months, although in 50% of patients some chorea may persist after 2 years, and recurrences may appear. A medical history of Sydenham's chorea seems to be a risk factor of development of chorea gravidarum or chorea related to use of oral contraceptives or antiepileptic drugs.
3. **Chorea-acanthocytosis (ChAc)**. This autosomal recessive disease is characterized by generalized chorea and severe orofacial dystonia with tongue and lip biting that produce orofacial self-mutilations. Neuropathy, subclinical or mild myopathy, and seizures, along with hepatic disease, are common associated features. X-linked inherited McLeod's syndrome has indistinguishable clinical findings, with otherwise less frequent orofacial dystonia, and more frequent seizures and severe hepatic failure.
4. **PKAN.** This disorder has onset during childhood, with the hallmarks of chorea and generalized dystonia that typically affect bulbar and orofacial muscles, with speech difficulties as a prominent clinical feature. Chorea and dystonia are associated with cognitive impairment and behavioral disorders, parkinsonian, and pyramidal tract features.
5. **Hyperglycemic-induced hemichorea–hemiballismus**. This condition occurs mostly in women, ranging from 50 to 80 years of age, and chorea develops in association with non-ketotic hyperglycemia in type 2 diabetes mellitus. Patients usually have no previous history of diabetes mellitus but develop choreic or ballistic movements on one side of the body, in the setting of elevated serum glucose levels (range of 400 to 1,000 mg/dl). CT scans may reveal a hyperdense lesion involving the right caudate and lentiform nucleus, but sparing the internal capsule, without mass effect. MRI scans reveal hyperintensity and hypointensity in the same structures in T1- and T2-weighted images, respectively. In most patients, lowering serum glucose levels to the normal range completely reverses the movements within 24 to 48 hours. In some cases, however, chorea persists after correction of the metabolic abnormality.

E. Differential diagnosis and evaluation. Although classification of chorea is based on etiology, differential diagnosis and evaluation of choreic patients are based primarily on age of onset.

1. **Adult-onset chorea.**
   a. Positive family history.
      (1) Genetic testing for Huntington's disease. Up to 25% of newly diagnosed HD patients have a negative family history due to non-paternity or ancestral death before disease manifestation.

   SCA 2, 3, and 17 must be considered when genetic testing for HD is negative.

      (2) Wilson's disease**.** See **evaluation of dystonia.**
   b. No family history.
      (1) MRI scan should be done in all cases to exclude vascular, neoplastic, infectious, or inflammatory pathology in the basal ganglia or adjacent structures.
      (2) **Rule out other causes of chorea.**
         (a) Pregnancy testing.
         (b) Review of medication record and drug abuse (**see classification**).
         (c) Metabolic and autoimmune disorders. Blood testing considering SLE, antiphospholipid antibody syndrome, thyrotoxicosis, or other metabolic disorders (**see classification**).
         (d) Polycythemia must be considered, especially in the elderly. Chorea associated with polycythemia seems to be related to blood hyperviscosity throughout the brain. Chorea may be the presenting symptom of polycythemia or

a sign of hematologic deterioration of the disease. Therapy with repeated phlebotomies may be an effective treatment of chorea in this condition.

(e) Diagnosis of ChAc must be suspected in young-adult patients with suggestive symptoms, even in the absence of family history. Analysis of acanthocytes in fresh blood samples has very low sensitivity, and repeated measurements must be done. Recently, determination of chorein in peripheral blood samples offers a markedly higher sensitivity and specificity for the diagnosis of ChAc. Western blot detection of chorein strongly supports the clinical diagnosis of ChAc when chorein is low or absent in the erythrocytes' membrane.

2. **Childhood-onset chorea.**
   a. **Positive family history.**
      (1) Wilson's disease**.** See **evaluation of dystonia.**
      (2) Genetic testing for Huntington's disease.
      (3) Genetic testing for benign hereditary chorea, usually associated with slowly progressive ataxia, should be investigated.
      (4) When there is a history of progressive cerebellar ataxia and choreoathetosis, with and without ocular motor apraxia, ataxia telangiectasia should be ruled out by measuring—fetoprotein in serum, even if telangiectasias are not observed in the conjunctiva, oral mucosa, or the skin.
      (5) Acanthocytes in blood testing. As acanthocytes are not specific of neuroacanthocytosis (also present in 10% of HDL2 and PKAN patients), they will not be ordered if neuroacanthocytosis is not clinically suspected.
   b. **No family history.**
      (1) MRI scan.
      (2) Sydenham's chorea. Antistreptolysin-O may be increased, but due to the long latency between streptococcus infection and the onset of chorea, most laboratory tests indicative of preceding streptococcal infection are not useful. Anti-DNase-B titers may be increased up to 1 year after the infection. Echocardiography may be very useful in supporting the diagnosis, when mitral valvulopathy is detected.
      (3) Rule out other autoimmune disorders like SLE and infectious chorea associated with viral (mumps, measles, and varicella) or postvaccination encephalitis.

IV. MYOCLONUS

A. Definition. Myoclonus is a clinical sign defined as sudden, brief, lightening-like, involuntary movements caused by muscular contractions or inhibitions. Muscular contractions produce so-called positive myoclonus, whereas muscular inhibitions produce negative myoclonus or asterixis.

B. Etiologic classification. In clinical practice, treatment of myoclonus is mainly based on the treatment of the underlying disorder. However, it can be also classified according to examination findings or neurophysiologic testing.

1. Physiologic myoclonus. Sleep jerks, anxiety induced, exercise induced, hiccups (singultus), and benign infantile myoclonus with feeding.
2. Palatal myoclonus. Idiopathic or symptomatic.
3. Epileptic myoclonus. Seizures dominate the disease.
   a. Epilepsia partialis continua.
   b. Idiopathic stimulus-sensitive myoclonus.
   c. Myoclonic absences in petit mal epilepsy.
   d. Childhood myoclonic epilepsy. Lennox–Gastaut's syndrome, Aicardi's syndrome, and juvenile myoclonic epilepsy (awakening myoclonus epilepsy of Janz).
4. Progressive myoclonus epilepsy. Baltic myoclonus (Unverricht–Lundborg) disease.
5. Symptomatic or secondarymyoclonus.
   a. Metabolic. Hyperthyroidism, hepatic failure, renal failure, dialysis syndrome, ion alterations (Na^+, K^+, Ca^{+2} and Mg^{+2}), hypoglycemia, non-ketotic hyperglycemia, metabolic acidosis, or alkalosis.

b. Infectious or post infectious. HIV, subacute sclerosing panencephalitis, progressive multifocal leukoencephalopathy, herpes simplex encephalitis, postinfectious encephalitis, malaria, syphilis, Cryptococcus, and Lyme's disease.
c. Hashimoto's encephalopathy.
d. Malabsorption. Celiac disease and Whipple's disease.
e. Other encephalopathies. Post hypoxia (Lance–Adams' syndrome), post-traumatic, and electric shock.
f. Drug-induced myoclonus. Tricyclic antidepressants, selective serotonin uptake inhibitors, monoamine oxidase inhibitors, lithium, antipsychotics, narcotics, anticonvulsants, anasthetics, contrast media, calcium channel blockers, antiarrhythmics, and drug withdrawal.
g. Basal ganglia degenerations. Wilson's disease, PKAN, Huntington's disease, MSA, CBD, PSP, and dentatorubropallidoluysian atrophy.
h. Dementias. Creutzfeldt–Jakob's disease, AD, DLB, frontotemporal dementia, and Rett's syndrome.
i. Focal **central** or **peripheral** nervous system damage. This category includes propriospinal or segmental spinal myoclonus.
j. Spinocerebellar degenerations. Ramsay–Hunt's syndrome, Friedreich's ataxia, and ataxia-telangiectasia.
k. Storage disease. Lafora's body disease, GM2 gangliosidosis, Tay–Sachs' disease, Gaucher's disease, Krabbe's leukodystrophy, ceroid-lipofuscinosis, and sialidosis.
l. Opsoclonus-myoclonus syndrome. Idiopathic, paraneoplastic (neural crest tumors).

C. Pathophysiology. Cortical mycolonus is produced by an imbalance between inhibitory and excitatory systems in the sensorimotor cortex rapidly conducting to the pyramidal tracts. Cortical myoclonic activity spreads relatively rapidly from an initial focus in one sensorimotor cortex to other ipsilateral sensorimotor cortical areas through corticocortical pathways and to the opposite sensorimotor cortex through the corpus callosum. Propriospinal myoclonus is explained by changes in spinal cord excitability, probably due to dorsal horn interneuron hyperactivity. In brainstem myoclonus, muscle jerks arise from activity in neuronal centers within the lower brainstem, probably involving the same circuitry as the normal startle reflex.

D. Selected clinical syndromes.

1. **Cortical myoclonus** is multifocal, but predominantly affects body parts with the largest cortical representations such as the hands and face. Patients with cortical myoclonus may have purely focal or multifocal jerks, but they may have additional bilateral or generalized jerks, suggesting the spread of excitatory myoclonic activity between the cerebral hemispheres and across the sensorimotor cortex. As the motor cortex is most involved in voluntary action, the jerks are usually most marked during action. Metabolic encephalopaties cause generalized and spontaneous myoclonus that, like other forms of myoclonus, is triggered or enhanced by sensitive stimuli (light touch or stretch lead to reflex jerks of the stimulated area). **Epilepsia partialis continua** is a myoclonic epilepsy caused by focal cortical lesions, and myoclonic rhythmic jerks usually occur in the hands or face. Rhythmic forms of the myoclonic jerks can be misinterpreted as tremor.
   a. **Differential diagnosis.**
      (1) Clonic tics.
      (2) Myokymia.
      (3) Startle syndromes (hyperekplexia).
      (4) Parkinsonian disorders. Mainly CBD.
      (5) Dementing conditions. Creutzfeldt–Jakob's disease, DLB, CBD, and AD.
   b. **Evaluation.**
      (1) MRI of the brain including the posterior fossa and the cervical spinal cord, to rule out structural lesions.
      (2) Blood tests, to rule out metabolic disturbances. Antithyrois antibodies, to rule out Hashimoto's encephalopathy.
      (3) Review of medication records.
      (4) EEG, to rule out epileptogenic discharges.
      (5) Lumbar puncture (LP), to rule encephalitis, Creutzfeldt–Jakob's disease, or post infectious encephalopathies (HIV and subacute sclerosing panencephalitis).

2. **Brainstem myoclonus.** Brainstem motor systems are particularly involved in axial and bilateral movements. Jerks in brainstem myoclonus are generalized, especially axial, with long-lasting electromyographic bursts (>100 ms) and may be provoked by many different types of sensory stimuli, although cutaneous taps around the nose and face are particularly effective. The hallmark is auditory reflex jerks, known as hyperekplexia.
   a. **Differential diagnosis.**
      (1) Brainstem structural lesions.
      (2) Startle syndromes.
      (3) Creutzfeldt–Jakob's disease.
   b. **Evaluation.**
      (1) MRI of the brain including, to rule out structural lesions.
      (2) Family history of startle syndrome.
      (3) LP.
3. **Propriospinal myoclonus**. Spinal segmental systems may become hyperexcitable, often by viral irritation or the isolation of anterior horn cells from inhibitory influences by disorders such as syringomyelia, glioma, or spinal ischaemia. The result is myoclonus involving one or two contiguous spinal myotomes. Propriospinal myoclonus leads to predominantly axial flexion and extension jerks that, unlike brainstem myoclonus, spare the face and are not provoked by sound. This form of myoclonus is usually caused by damage to the spinal cord through cervical trauma, inflammation, or a tumor.
   a. **Evaluation.**
      (1) MRI of the cervical, thoracic, and lumbar spine to rule out structural lesions.
      (2) Evaluation for multiple sclerosis.
      (3) Personal history of cervical trauma.
4. **Palatal myoclonus**. This nomenclature is historically respected but phenomenologically inaccurate, and more properly it should be designated as palatal tremor. Palatal movements are fast and rhythmic and can spread to the throat, face, and diaphragm. Patient may hear an "ear-click," due to contraction of the tensor veli palatini muscle. Palatal myoclonus/tremor may be idiopathic or symptomatic. Although the presence of the ear-click had been classically associated with the idiopathic cases, it can be also present in secondary cases, in patients with structural brainstem lesions. Idiopathic cases have been related to hypertrophy of the inferior olive, and symptomatic cases to lesions (ischemic, neoplastic, and inflammatory) in the triangle of Guillain–Mollaret, which includes the red nucleus, the inferior olive, and the dentate nucleus.
   a. **Evaluation.** MRI of the brain including the posterior fossa to rule out structural lesions involving the triangle of Guillain–Mollaret.
5. **Post hypoxic action (intention) myoclonus, or Lance–Adams' syndrome**. This form of cortical myoclonus occurs in survivors of anoxic brain injuries. The jerks are triggered by voluntary movement, and specially, when movements are directed to a particular goal or target. Action-intention myoclonus is the most disabling form of myoclonus associated with provocative factors, with jerks that prevent or disrupt the movement. The myoclonic movements range from simple, localized focal jerks to generalized, disabling jerks.

V. TICS

A. Definition. Tics are brief, intermittent, and repetitve, involuntary or semivoluntary movements and sounds. They are preceded by an urge or sensation in the affected muscle group and a sense of temporary relief once the movement is performed. Although tics may resemble other types of hyperkinetic movements (e.g., myoclonus and dystonia), the urge is considered a key characteristic that suggests that the movement is a tic. The patient's ability to transiently suppress the movements by conscious effort and an increased frequency of tics after efforts to suppress have ceased are additional supportive features of the diagnosis. Onset of tic disorders usually occurs during childhood (before age 18).

B. Phenomenologic classification.

1. Anatomic distribution.

a. Simple motor tics. Focal movements involving one group of muscles (eye blinking, mouth movements, and shoulder elevation).
b. Complex motor tics. Coordinated or sequential patterns of movement involving various groups of movements. They may resemble usual motor tasks or gestures (jumping and throwing) and include echopraxia (imitating others' gestures) and copropraxia.
c. Simple phonic tics are elementary, meaningless noises or sounds (sniffing, grunting, clearing the throat, coughing, and belching).
d. Complex phonic tics are meaningful syllables, words, or phrases ("okay" and "shut up") and include pallilalia, echolalia, and coprolalia.
e. Sensory tics are uncomfortable sensations (pressure, cold, warmth, or paresthesias) localized to certain body parts that are relieved by the performance of an intentional act in the affected area.

2. Speed of movement.

a. Clonic tics are brief, sudden, and jerk-like.
b. Dystonic tics involve sustained twisting, or posturing is present.
c. Tonic tics involve tensing contraction of muscles (abdominal or limb muscles).

3. Natural history.

a. Transient tic disorder. Multiple motor and/or phonic tics with duration of at least 4 weeks, but <12 months. These tics occur in 20% of children during the first decade of life.
b. Chronic tic disorder. Single motor and/or phonic tics, but not both, which are present for >1 year.
c. Tourette's syndrome. Both motor and phonic tics are present for >1 year.

C. Etiologic classification.

1. Primary.
   a. Tourette's syndrome, transient tic disorder, and chronic tic disorder.
2. Secondary.
   a. Hereditary disorders with tics as one manifestation of another primary neurologic condition. Huntington's disease, neuroacanthocytosis, PKAN, Wilson's disease, and tuberous sclerosis complex.
   b. Infections. Encephalitis, neurosyphilis, and Sydenham's chorea.
   c. Drugs. Methylphenidate, antiepileptic drugs, dopamine receptor blocking drugs (see tardive syndrome), psychostimulant drugs (amphetamines, pemoline and cocaine), and levodopa.
   d. Head trauma.
   e. Toxins. Carbon monoxide.
   f. Developmental. Autistic spectrum disorders (Rett's syndrome and Asperger's syndrome), intellectual disability syndromes, chromosomal disorders (Down's syndrome, Klinefelter's syndrome, fragile X syndrome, and triple X).
   g. Focal brain lesions. Stroke and multiple sclerosis.

D. Pathophysiology. Dopaminergic imbalance in the ventral part of the cortico–striatal–thalamocortical pathways (medial prefrontal cortex connecting to the ventral striatum—ventral part of the globus pallidus, and the dorsomedial thalamus) is involved in the expression of tics. However, some data suggest an associated cortical dysfunction in Tourette's syndrome. In volumetric and functional MRI studies, children with TS have shown larger dorsolateral prefrontal regions, increased cortical white matter in the right frontal lobe, and activation of the prefrontal cortex related to tic suppression. Likewise, transcranial-magnetic-stimulation studies suggest that tics originate from impaired inhibition in the motor cortex.

E. Selected clinical syndromes.

1. **Tourette's syndrome**. Tourette's syndrome is characterized by multiple motor tics plus one or more phonic tics that wax and wane over time. Diagnosis is made according to the *DSM-IV* clinical criteria.
   a. Multiple motor and one or more phonic tics (not necessarily concurrently).
   b. Onset before age 21 years.

c. Variations in anatomic location, number, frequency, complexity, and severity of the tics occur over time.
d. Tics occur many times a day, nearly every day or intermittently for more than a year, with symptom-free intervals not exceeding 3 months.
e. Tics are not related to intoxication with psychoactive substances or CNS disease (e.g., encephalitis).
f. Tics cause distress to the patient.

The average age at the onset of tics is 5 years, become more severe at 10 years of age, but half of patients are free of tics by 18 years. Although tics may persist into adulthood, their severity is gradually diminished.

Tourette's syndrome is commonly associated with behavioral comorbidities such as attention deficit-hyperactivity disorder (15% to 50%), obsessive compulsive disorder (35% to 45%), addictive and aggressive behaviors (related to poor impulse control), anxiety, depression, and decreased self-esteem. Obsessive-compulsive symptoms in Tourette's syndrome are characterized by ritualistic behaviors, and need for completion, symmetry, and perfection. In severe cases, self-injurious behaviors may be also present.

a. **Differential diagnosis.**
   (1) Myoclonus **(see above).**
   (2) Huntington's disease, neuroacanthocytosis, and PKAN.
b. **Evaluation.**
   (1) MRI of the brain to rule out structural brain lesions or to disclose images suggesting a metabolic disorder, if neurologic examination demonstrates other findings besides tics.
   (2) Review of medication record for drug exposure.
   (3) History of drug exposure (psychostimulant drugs).
   (4) Genetic testing for Huntington's disease if other neurologic symptoms are present (cognitive impairment and ataxia).
   (5) Review of family background for other examples of tics, attention deficits, or OCD.

VI. TARDIVE SYNDROMES

A. Definition. Tardive syndromes refer to a group of disorders characterized by persistent abnormal involuntary movements caused by chronic exposure to a dopamine receptor blocking drug within 6 months of the onset of symptoms and persisting for at least 1 month after stopping the offending drug.

Tardive syndromes cover the gamut of hyperkinetic movement disorders, often with multiple types. Choreic and stereotypic bucco-linguo-masticatory dyskinesias are characterized by repetitive and predictable or unpredictable movements involving the oral, buccal, and lingual areas (tongue twisting and protusion, lip smacking or elevation, and chewing). Dystonic facial grimacing, neck and trunk arching movements are also common and can mix with choreic movements. Myoclonus, tics, and restless purposeful movements (akathisia) have also been related to chronic exposure to dopamine receptor blocking agents. Tardive tremor has been described but is controversial, and parkinsonism in a patient on neuroleptic medication is usually due to an increased dose of neuroleptic (drug-induced parkinsonism), and therefore not considered a tardive syndrome. Tardive syndromes may occur on steady doses of dopamine receptor blocking agents or also induced by withdrawal.

B. Drugs reported to cause tardive syndromes.

1. Neuroleptic drugs. Haloperidol, risperidone, olanzapine, chlorpromazine, pimozide, levomepromazine, thioridazine, tiapride, fluphenazine, perphenazine, among others.
2. Anxyolitics. Flupenthixol and melitracene.
3. Calcium channel blocker. Cinnarizine and flunarizine.
4. Dihydropiridines. Amlodipine, nifedipine, and nimodipine.
5. Antiemetic drugs. Metoclopramide, clebopride, and cinitapride.
6. Anti-dizziness drugs. Tietilperazine, sulpiride, amisulpride, and veralipride.
7. Trimetazidine.

C. Risk factors for tardive dyskinesia.

1. Age older than 65 years.
2. Female sex.
3. Concomitant extrapyramidal symptoms.
4. Basal-ganglia lesions on neuroimaging.

D. Selected clinical syndromes.

1. Typical orofacial buccolingual dyskinesia.
2. Tardive dystonia. This syndrome may be indistinguishable from idiopathic dystonia and can be focal, segmental, or generalized. The movement can improve with sensory tricks. However, contrary to idiopathic dystonia, tardive dystonia often improve with voluntary action such as walking. When involving the neck, predominates retrocollis, and when the trunk is affected, predominates tonic lateral flexion of the trunk (Pisa syndrome or pleurothotonus), or bench arching (opisthotonus).
3. Tardive akathisia. Akathisia is characterized by a feeling of inner restlessness. Subjectively, the most common complaint is the inability to keep the legs still and feeling fidgety, but patients can also describe a vague inner tension or anxiety. Objectively, patients are seen rocking from foot to foot, walking in place while sitting, and, occasionally, grunting, or trunk rocking. Characteristically, akathisia may improve with low doses of propranolol.

Recommended Readings

Berardelli A, Rothwell JC, Hallett M, et al. The pathophysiology of primary dystonia. *Brain*. 1998;121:1195–1212.

Bhatia K, Marsden MD. The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain*. 1994;117:859–876.

Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol*. 2004;3:598–607.

Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. *Mov Disord*. 1998;13(suppl 3):2–23.

Deuschl G, Elble R. Essential tremor—neurodegenerative or nondegenerative disease. Towards a working definition of ET. *Mov Disord*. 2009;14:2033–2041.

Dobson-Stone C, Velayos-Baeza A, Filippone LA, et al. Chorein detection for the diagnosis of chorea–acanthocytosis. *Ann Neurol*. 2004;56:299–302.

Ferioli S, Dalmau J, Kobet CA, et al. Anti-N-methyl-D-aspartate receptor encephalitis: characteristic behavioral and movement disorder. *Arch Neurol*. 2010;67:250–252.

Fernandez HH, Friedman JH. Classification and treatment of tardive syndromes. *Neurologist*. 2003;9:16–27.

Geyer HL, Bressman SB. The diagnosis of dystonia. *Lancet Neurol*. 2006;5:780–790.

Louis ED. Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. *Lancet Neurol*. 2010;9:613–622.

Rubio-Agustí I, Dalmau J, Sevilla T, et al. Isolated hemidystonia associated with NMDA receptor antibodies. *Mov Disord*. 2011;26:351–352.

Singer HS. Tourette's syndrome: from behaviour to biology. *Lancet Neurol*. 2005;4:149–159.

Walker RH, Jung HH, Dobson-Stone C, et al. Neurologic phenotypes associated with acanthocytosis. *Neurology*. 2007;68:92–98.

Wild EJ, Tabrizi SJ. The differential diagnosis of chorea. *Pract Neurol*. 2007;7:360–373.

CHAPTER

29 Approach to the Hypokinetic Patient

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Hypokinesia is defined as a decrease in the amount and amplitude of both volitional and automatic movements and is almost always associated with *bradykinesia* (slowness of movement). The term *akinesia* is sometimes used to imply a severe reduction in the amount or amplitude of movement. *Parkinsonism* refers to a motor syndrome with the following cardinal features: bradykinesia, rigidity, rest tremor, and postural instability. Idiopathic Parkinson's disease (IPD) is the most common cause of *parkinsonism*. Other forms of *parkinsonism* are histologically different and often accompanied by additional neurologic signs and symptoms (Fig. 29.1).

Through careful questioning, clinicians can distinguish a history of neuromuscular weakness from a movement disorder causing parkinsonism such as IPD. It is also essential to determine whether slowness or lack of movement is caused by a psychiatric disorder (catatonia or severe depression), neuromuscular condition producing stiffness (e.g., stiff person syndrome), endocrine disorder such as hypothyroidism with resulting global slowing, or a rheumatologic condition such as ankylosing spondylitis with mechanical restriction of movements.

I. EVALUATION OF PARKINSONISM: HISTORY

A. Direct motoric manifestations of parkinsonism. What a patient perceives as weakness or poor balance may actually be a manifestation of hypokinesia. Conversely, slowness in performing motor functions such as dressing, walking, feeding, or writing may actually relate to incoordination, weakness, or dementia. Difficulty in rising from a chair, hesitancy in initiating gait, and a change in the legibility and size of handwriting, falls, freezing, hypophonia, and hypomimia are common symptoms of hypokinesia.

Rest tremor, stiffness (rigidity), and postural imbalance in the absence of other neurologic complaints suggest an IPD. On the other hand, the association of hypokinesia/bradykinesia with neurologic symptoms outside the motor realm usually suggests a condition other than IPD. Such symptoms include seizures, sensory loss, paresthesias, headache, early dementia, visual loss, apraxia, and early or severe autonomic symptoms such as impotence, orthostatic hypotension, or urinary incontinence. Another useful historical fact in differentiating IPD from other forms of parkinsonism is the sequence in which otherwise typical parkinsonian symptoms appear. Although postural imbalance and severe gait disturbance often appear late in the course of IPD, their appearance as presenting symptoms in a hypokinetic patient suggest a different etiology of parkinsonism.

B. Response to medications. Absence of benefit from adequate dosages of dopaminergic drugs, especially levodopa, casts doubt on the diagnosis of IPD and suggests a diagnosis of secondary causes of parkinsonism or one of the Parkinson's-plus syndromes. Equally important is determining whether, early in the illness, these medications produced psychiatric side effects such as hallucinations or autonomic symptoms such as severe orthostatic hypotension. The former suggesting the possibility of dementia with Lewy's bodies (DLB), and the latter indicating possible multiple system atrophy (MSA). In IPD, psychiatric and autonomic side effects from dopaminergic drugs are not uncommon but usually appear when the illness is at least moderately advanced.

C. Cognitive symptoms. Even early in the course of the disease process, patients with IPD may have mild executive and visuospatial dysfunction. Frank dementia is more common among older patients and usually after the illness is moderately advanced. Mild to moderate cognitive symptoms are present in most of the Parkinson's-plus

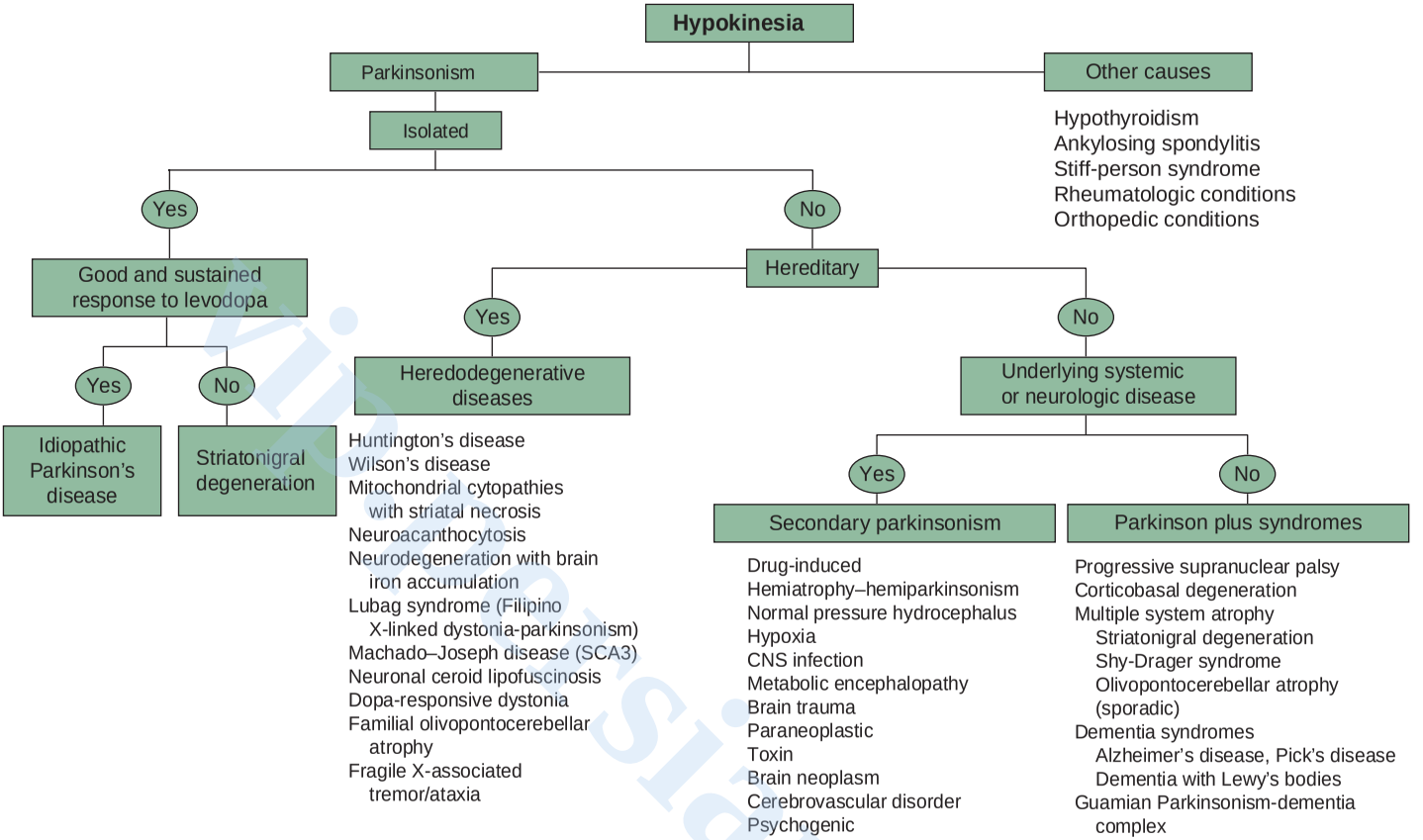

FIGURE 29.1 Algorithm for differential diagnosis of hypokinesia.

syndromes but are seldom the presenting symptom. Severe, early cognitive abnormalities may indicate a primary dementing disorder such as Alzheimer's disease (AD) or vascular dementia.

D. **Psychiatric symptoms**. Symptoms suggestive of depression or anxiety may precede the onset of IPD. If hallucinosis (typically visual) is present, determine if it began early or late in the course of the illness and whether it appeared in response to the institution or escalation of an antiparkinson drug. Very early appearance of hallucinations in cases of parkinsonism or their presence in an untreated parkinsonian patient raises the probability of DLB.

E. **Sleep disorders**. The rapid eye movement behavior may precede the onset of parkinsonism by several years in IPD or DLB. Restless legs syndrome and/or periodic limb movements of sleep may be associated with IPD. Discomfort because of rigidity and inability to turn in bed can cause sleep fragmentation (see Chapters 9 and 55).

F. **Dysautonomia.** Constipation, urinary urgency, impotence, and orthostasis may accompany or even precede IPD. When prominent early, these symptoms may suggest MSA.

G. **Medication usage**. Patients must be asked if they are currently taking or have recently received antidopaminergic drugs such as neuroleptics, reserpine, or metoclopramide. In addition any history of illicit drug use should be ascertained.

H. **Family history**. IPD has a complex and multifactorial etiology. Patients with Mendelian pattern of inheritance constitute a small minority of the overall Parkinson's disease (PD) population. Heritable disorders that can mimic PD include Wilson's disease (autosomal recessive), juvenile Huntington's disease (HD; autosomal dominant), and essential tremor (ET; autosomal dominant with variable penetrance).

I. **Toxic exposure**. Exposure to toxins such as manganese or carbon monoxide must be ascertained because both can result in parkinsonism. Less common causes include mercury, carbon disulfide, methanol, and cyanide.

II. PHYSICAL EXAMINATION

A. The clinical findings of parkinsonism.

1. **Hypomimia** is characterized by diminished facial expression with infrequent eye blinking. *A fixed facial expression*, often seen in progressive supranuclear palsy (PSP), consists of an unchanging expression such as surprise in which the forehead may be furrowed, the eyelids retracted, and the nasolabial folds deepened. *Myerson's sign*, present in IPD and a variety of other basal ganglia disorders, consists of persistent reflex eyelid blinking to repetitive finger taps applied to the glabella, instead of the normal rapid habituation after the fourth or fifth tap.
2. **Hypophonia** is characterized by diminished amplitude and inflection of speech. *Tachyphemia* is an excessively rapid speech pattern, which is a common accompaniment of hypophonia, making such speech even more unintelligible.
3. **Rigidity** may be predominant in axial muscles (e.g., neck or trunk), in the limbs, or equally severe in both. Increased resistance to passive movement of the involved body part is easily appreciated when rigidity is severe. When subtle, rigidity can be reinforced by asking the patient to alternately open and close the fist of the hand on the side opposite of the arm or leg being tested. The presence of tremor in the same limb demonstrating rigidity gives rise to a rachet-like sensation referred to as *cogwheel rigidity*.
4. **Tremor** may appear in one or more forms in patients with parkinsonism.
   a. **Resting tremor** is the hallmark of IPD. Its absence casts some doubt on the diagnosis but certainly does not rule it out. It is also present in some other forms of parkinsonism. The tremor is most commonly seen in the hands and to a slightly lesser extent in the lower extremities and mandible. **Rest tremor** rarely involves the head and never affects the voice. It appears at a frequency of 4 to 5 Hz and is often at least temporarily extinguished by volitional movement. A subtle tremor can be uncovered by asking the patient to perform difficult mental arithmetic, a mildly stressful task.
   b. **Action tremor** may also be present in IPD as well as in other parkinsonian syndromes, especially those associated with cerebellar dysfunction. It can be present as a *postural tremor* while the arms are outstretched in front of the patient or as a *kinetic*

tremor while the patient is performing a task such as the finger-to-nose test. Postural tremor alone, in the absence of parkinsonian signs, suggests a diagnosis of ET.

c. **Positional tremor**. Some tremors are particularly prominent when the involved body part is placed in a specific position. The *wing beating tremor* of Wilson's disease is an example of this phenomenon. This tremor is noted when the arms are abducted at the shoulders while flexed at the elbow.

5. **Bradykinesia** can be documented by simply observing the speed, amplitude, and amount of ordinary movements made by the patient such as gestures or shifting of body position. Repetitive motion tasks such as tapping the index finger against the thumb demonstrate slowness of movement and a progressive loss of amplitude.
6. **Impairment of automatic movements** is noticeable as a decrease in gesticulation and head movement during conversation, a reduction in the automatic repositioning of limbs while sitting in a chair or reclining in bed, and as a decrease in the amplitude of arm swing while walking. In severe hypokinesia, the affected arm(s) may not swing at all, but rather be held in a semiflexed posture across the trunk.
7. **Impairment of repetitive movements** such as handwriting or buttoning a shirt is not only performed slowly, but the amplitude of each successive movement typically becomes progressively smaller. This may account for the progressively smaller letters (micrographia) seen when a hypokinetic patient is asked to write a long sentence.
8. **Impaired initiation of movement** is manifested by difficulty in arising from a chair or hesitancy in taking the first step while attempting to walk. Many patients with IPD have difficulty initiating two motor acts simultaneously such as standing up and shaking hands. Rising from a chair is tested by asking the patient to rise with arms crossed in front of the body to prevent pushing off. The patient may require several attempts to succeed or may be totally unable to arise without using his arms. If the patient is unable to rise without assistance, a judgment must be made as to whether the cause is weakness (which can be tested independently).
9. **Gait and posture** should be evaluated by having the patient walk a distance of at least 20 feet in an area free from obstacles. Parkinsonian patients often display reduced stride length and arm swing, stooped posture, difficulty in initiating gait, and turns with the body moving as a single unit (en bloc). In more advanced cases, progressively more rapid, small steps as the body leans forward (festination) and "freezing" in mid gait may be observed.
10. **Freezing** is a sudden involuntary cessation of a motoric act, usually walking, while other functions remain intact. This phenomenon is confined to basal ganglia disorders. It may occur spontaneously or may be provoked by external circumstances such as attempting to turn mid gait or pass through a narrow space such as a doorway. Emotional stimuli including anger or fear can provoke freezing as can the prospect of entering a room filled with people. A variety of sensory or motor tricks such as marching to a cadence are effective in overcoming freezing.
11. **Postural reflexes** are evaluated by asking the patient to establish a comfortable base, with feet slightly apart and then, while standing behind the patient, applying a brisk backward sternal perturbation. A normal response is to take up to one corrective step backward to prevent falling. When postural reflexes are impaired, more than one step will be needed before balance is reestablished. When postural reflexes are absent, the patient will continue to reel backward and fall if not checked by the examiner.

B. **Non-Parkinsonian neurologic signs.** Several neurologic findings are associated with one or more forms of atypical parkinsonism, but most of these signs are uncommon in IPD.

1. **Apraxia** should be tested independently in both upper extremities. The patient should be asked to perform such tasks as saluting, throwing a kiss, or demonstrating how to use an imaginary tooth brush. Inability to perform these tasks in the face of normal strength and coordination, or the use of a body part such as a finger in place of an imagined implement, suggest apraxia. Apraxia and parkinsonism can be seen in cases of corticobasal degeneration (CBD) and AD.
2. **Cortical sensory functions** such as graphesthesia, stereognosis, and tactile localization are sometimes abnormal in CBD.
3. **The alien limb phenomenon** is present when a patient manifests uncontrollable grasping and manipulating of objects or when a hand exhibits interfering involuntary

movement with one of the other limbs (inter manual conflict). This phenomenon may be present in CBD, ischemic strokes, or Creutzfeldt–Jakob's disease (CJD).

4. **Ocular motility abnormalities.** Inability to generate normal saccadic eye movements, especially downward, with preservation of the same movements when eliciting the oculocephalic reflex indicates a *supranuclear gaze palsy*. This finding is most characteristic of PSP but can be found in other forms of atypical parkinsonism as well. It is important to remember that limited upgaze is not an uncommon finding in the normal elderly patient, but impaired downgaze is always abnormal. Excessive *macro square wave jerks*, spontaneous repetitive small horizontal oscillations of the eyes from the midline, are also seen in PSP.
5. **Reflex myoclonus**, elicited by tapping the arm, leg, or fingertip with the examiner's own fingertip or with a percussion hammer, may be present in cases of CBD.
6. **Blood pressure** must be measured in the recumbent and standing positions while recording the concurrent heart rate. Orthostatic hypotension is an early and common manifestation of MSA but occurs later in the course of IPD, especially with the use of dopaminergic or anticholinergic drugs.
7. **Mental status evaluation.** Evaluation should include functions such as immediate and short-term recall, orientation, constructional praxis, calculation, and comprehension of three-step commands.
8. **Other neurologic signs**. In order to determine the full extent of involvement of the CNS, a complete neurologic examination should be performed to establish the presence of hyperactive or hypoactive muscle stretch reflexes, sensory loss, cranial nerve dysfunction, cerebellar signs, pathologic reflexes (especially Babinski's sign), weakness, or muscle atrophy.

III. LABORATORY STUDIES

A. Neuroimaging.

1. **IPD.** In classical IPD where the diagnosis is strongly suggested by the history and physical examination, neuroimaging is not necessary. IPD is commonly asymmetric, but if symptoms or signs of parkinsonism are remarkably asymmetric resulting in severe involvement on one side and virtually no involvement on the other, a CNS imaging study, preferably MRI, is indicated to evaluate for the possibility of unilateral structural basal ganglia pathology such as a neoplasm, arteriovenous malformation, infarction, or the presence of brain hemiatrophy.
2. **Other forms of parkinsonism.** In patients with insufficient findings to make a diagnosis of IPD (e.g., a patient with hypokinesia only) or with additional neurologic findings not usually seen in IPD, a brain imaging procedure is indicated, preferably an MRI. Not all degenerative forms of parkinsonism are associated with demonstrable MRI abnormalities and those that are may demonstrate the characteristic abnormality infrequently or only in the advanced stages of the illness (see Section V-C instead of VIII-C). Therefore, a normal MRI or CT scan of the brain does not rule out syndromes such as PSP or MSA but does usually rule out normal pressure hydrocephalus (NPH), brain tumor, or stroke.

B. Laboratory and genetic tests are not useful in establishing a diagnosis of IPD except in few genetic forms, but can be of benefit in diagnosing several other causes of parkinsonism (see Section V-G instead of VIII).

IV. DIFFERENTIAL DIAGNOSIS

A. IPD. This is the most common cause of parkinsonism with a prevalence 0.2% and increasing with age (4% among those patients older than 80 years). IPD is a degenerative disorder of unknown but probable multifactorial etiology, with genetics likely conferring susceptibility to the effects of the environment and aging in most cases. More than 10 mutations (e.g., Parkin, PINK1, and LRRK2) with Mendelian pattern of

inheritance have been identified, leading to an IPD picture ranging from young onset with some atypical features to typical presentation and course in old age. Yet, patients with single-gene disorders constitute a small minority of the overall PD population. Consideration of single-gene inheritance is most important in young onset patients. Metabolic dysfunction of mitochondrial complex I has been demonstrated in PD, whether acquired or hereditary. The predominant abnormality is in the substantia nigra pars compacta and nigrostriatal pathway leading to dopamine deficiency in the striatum. The wide spectrum of symptoms and the resistance of some non motor symptoms (such as depression, sleep disorders, cognitive impairment, and autonomic dysfunction) to levodopa support the pathologic observations that the degenerative process also involves other brainstem nuclei and subcortical structures.

1. **Clinical.** The cardinal symptoms are resting tremor, bradykinesia, rigidity, and impairment of postural reflexes. The onset is usually asymmetric, and tremor is the most common presenting sign. Postural instability, gait difficulty, and dysautonomia appear with progression of the disease. Depending on the age of the cohort and follow-up period, 30% to 78% of patients have been reported to develop dementia, but it is seldom severe and is never a presenting symptom. The incidence of an IPD increases sharply with age, although it can present at any age. Arbitrarily, patients with onset between ages 21 and 39 are classified as young-onset IPD. They exhibit a more gradual progression of symptoms and are more likely to experience dystonia as an early sign. Levodopa-induced dyskinesias and motor fluctuations that can occur in IPD at any age are more frequently observed in this age group. The differential diagnosis of juvenile parkinsonism (before the age of 21) is broad and includes hereditary and metabolic conditions.
2. **Neuroimaging.** MRI and CT of the brain are usually unremarkable in IPD. A positron emission tomography (PET) scan shows decreased fluorodopa uptake in the striatum but no striatal abnormality in fluorodeoxyglucose scans. Single photon emission computed tomography (SPECT) shows decreased dopamine transporter density.
3. **Neuropathology.** Lewy's bodies (eosinophilic intra cytoplasmic inclusions), mainly in the substantia nigra, are the pathologic hallmark of this disorder. In IPD, these inclusions stain for alpha-synuclein, the protein produced by the mutant gene in the rare autosomal dominant form of PD.
4. **Other tests.** There is no specific test for the diagnosis of IPD.

B. **Secondary parkinsonism.** Parkinsonism can be induced by a wide spectrum of disease processes affecting the brain, especially the basal ganglia. These include infection, cerebrovascular disorders, toxins, metabolic disorders, trauma, neoplasm, drugs, hypoxemia, and hydrocephalus. Selected causes include the following:

1. **Drug-induced parkinsonism.** Neuroleptics and metoclopramide block striatal D-2 dopamine receptors, whereas reserpine depletes dopamine from presynaptic vesicles. Each of these drugs can result in motoric symptoms indistinguishable from IPD. The "atypical" neuroleptic clozapine mainly blocks extrastriatal (D-4) receptors and does not cause parkinsonism; quetiapine, also seems to have a low potential to cause this adverse effect. Other atypical neuroleptics, such as risperidone, olanzapine, aripiprazole, can cause parkinsonism. An underlying predisposition to PD may be in part responsible for the emergence of this syndrome. The resolution of drug-induced parkinsonism may take several months after discontinuation of the offending medication.
2. **Normal pressure hydrocephalus (NPH).**
   a. **Clinical.** This is a form of communicating hydrocephalus. Approximately one-third of patients with this disorder have a history of spontaneous or traumatic subarachnoid hemorrhage or meningitis. Although, as measured by lumbar puncture, the CSF pressure is normal, there is excessive force on the walls of the dilated lateral ventricles, especially the frontal horn, leading to the compression of surrounding structures. The clinical triad of NPH consists of gait apraxia (magnetic gait), subcortical dementia (which may later include cortical features), and urinary incontinence, often appearing late in the illness. The hesitant gait may resemble that seen in IPD, but the absence of rest tremor, the appearance of incontinence, and the absence of significant benefit from levodopa allow the two conditions to be distinguished. Early recognition of this syndrome is important because in some cases shunting the ventricles can reverse it (see Chapter 8).

b. **Neuroimaging.** Enlarged lateral ventricles, especially the frontal and lateral horns, which are disproportionate to cortical atrophy, are seen. A proton density MRI demonstrates periventricular hyperintensity suggesting transependymal flow.
c. **Other tests.** Fisher's test consists of removing 30 to 50 cc of CSF and observing for improvement in symptoms over the next 24 hours. It is a useful test and does not require sophisticated laboratory techniques. Intracranial pressure monitoring allows demonstration of periods of high CSF pressure (b-waves) and is used widely as a predictor of response to shunting.

3. **Hemiatrophy–hemiparkinsonism.** These patients present at a relatively early age with markedly asymmetric parkinsonism affecting the side of their body manifesting hemiatrophy. They may have a history of abnormal birth and contralateral hemisphere hemiatrophy, both of which raise the possibility of an early childhood brain insult, which later in life manifests as delayed-onset parkinsonism. The slow progression of this disorder, its occasional association with dystonia, and the striking asymmetry form the basis of its distinction from IPD.
4. **Toxins.**
   a. *Carbon monoxide* (CO). Acute or chronic CO poisoning causes globus pallidus or striatal necrosis. The onset of parkinsonism can be immediate after the incident, but more commonly develops days to weeks after an initial recovery from coma. Response to levodopa is poor or absent.
   b. *Manganese* intoxication can result in a parkinsonian state, and in addition is often associated with unusual behavioral symptoms such as hallucinations and emotional lability or other movement disorders such as dystonia.
   c. *Cyanide* and *methanol* intoxication can also cause bilateral basal ganglia necrosis and parkinsonism.
5. **Cerebrovascular disease.** Either a lacunar state with multiple small infarcts of the basal ganglia or subacute arteriosclerotic encephalopathy affecting basal ganglia connections can lead to parkinsonism. In either condition, dementia is also common. Resting tremor is usually absent in these patients. Gait disorder can be very prominent and occasionally constitutes the only neurologic symptom, giving rise to the term "lower-body parkinsonism." The response to levodopa is limited, but occasional patients do show benefit.
6. **Trauma.** Pugilistic encephalopathy is a progressive neurologic syndrome characterized by parkinsonism, dementia, and ataxia. It is seen in boxers with a history of repeated head trauma. Treatment is usually unsatisfactory.

   Focal acute injury to the midbrain and substantia nigra and subdural hematoma are two other possible causes of post-traumatic parkinsonism.

C. Parkinson-plus syndromes. This is a group of parkinsonian syndromes distinguished from IPD by the presence of additional prominent neurologic abnormalities. In these conditions, there may be cerebellar, autonomic, pyramidal, oculomotor, cortical sensory, bulbar, cognitive, and psychiatric dysfunction, as well as apraxia and movement disorders not typically seen in untreated IPD such as myoclonus, dystonia, or chorea. Any of these neurologic or psychiatric abnormalities can appear early in the course of the illness. Early falls with gait disturbance or postural instability, absence of resting tremor, early dementia, and supranuclear gaze palsy are signs that should always prompt consideration of a parkinson-plus syndrome. The parkinsonian components of these disorders such as akinesia and rigidity are usually not responsive to levodopa, although early transient responsiveness can be observed. The onset of these diseases is generally in the fifth or sixth decade of life with average survival of 5 to 10 years. The cause of death is usually pneumonia, other intercurrent infections, or sepsis. The etiology of this entire group of disorders is largely unknown.

Despite the apparent clinical differences between IPD and the parkinson-plus syndromes, differentiation between the two can be difficult. In a clinicopathologic study, 24% percent of patients who were clinically diagnosed with IPD were found to have a different type of parkinsonism at autopsy. In parkinson-plus syndromes, the brain MRI can occasionally be helpful. An EEG may show nonspecific abnormality such as slowing of the background activity. The specific clinical and imaging features of individual parkinson-plus syndromes are described below. Although each of these conditions has

characteristic clinical findings, it is important to remember that there is significant overlap in signs and symptoms among them.

1. **PSP.**
   a. **Clinical.** Early onset of gait difficulty, loss of postural reflexes resulting in backward falls, and freezing of gait, coupled with supranuclear gaze palsy (initially downgaze) are suggestive of PSP. Axial rigidity and nuchal dystonia with extensor posture of the neck, generalized bradykinesia, "apraxia" of eyelid opening and closing, blepharospasm, a furrowed forehead leading to a fixed facial expression, and a monotonous, but not hypophonic voice are additional features suggesting the diagnosis. There is variable, but often mild, cognitive decline, especially in executive functions. The presence of prominent bradykinesia in association with the fixed facial expression raises the possible diagnosis of IPD in these patients, but the ocular motility abnormalities, the early gait instability, the frequent absence of tremor, and the absence or loss of levodopa response suggest the correct diagnosis.
   b. **Neuroimaging.** Midbrain and, later, pontine atrophy are sometimes apparent on MRI.
   c. **Neuropathology.** PSP is a tauopathy. Globose neurofibrillary tangles composed of tau filaments are present affecting mainly the cholinergic neurons of the basal ganglia and brainstem nuclei with apparent sparing of the cortex.
2. **CBD.**
   a. Clinical. This syndrome can present as a strikingly asymmetric or unilateral akinetic-rigid syndrome associated with limb apraxia, alien limb phenomenon, cortical sensory signs, stimulus sensitive myoclonus, dystonia, and postural or action tremor. Supranuclear gaze palsy, cognitive impairment, and pyramidal tract signs can also be seen.
   b. Neuroimaging. MRI or CT of the brain are abnormal in some patients and reveal asymmetric frontoparietal atrophy.
   c. Neuropathology. CBD is also a tauopathy. Neuronal loss and gliosis are found in the frontoparietal regions and substantia nigra pars compacta. Swollen achromatic neurons and basophilic nigral inclusions, which represent an overlap with Pick's disease, are characteristic. Abundant cytoplasmic inclusions consisting of aggregated hyperphosphorylated tau protein are found.
3. **MSA.**
   a. **Clinical.** MSA consists of three syndromes that can present individually or in various combinations.
      (1) Striatonigral degeneration (SND). In this syndrome, an akinetic-rigid parkinsonism is predominant, but tremor is seldom present. SND is usually not responsive to levodopa because the degenerative process involves the postsynaptic dopamine receptors.
      (2) Sporadic olivopontocerebellar atrophy (OPCA). Cerebellar signs, especially ataxia and dysarthria are prominent findings in this syndrome, although they seldom exist in isolation. Other associated signs include gaze palsies, hyperreflexia, extensor plantar responses, and most importantly, features of parkinsonism.
      (3) Shy–Drager's syndrome (SDS). In SDS, there is dysfunction of the autonomic nervous system resulting in disabling orthostatic hypotension, bowel and bladder dysfunction, and impotence.

      It is not clear whether these disorders are distinct entities or represent different clinical presentations of the same basic condition, but they commonly occur together and share pathologic features (see below). From a diagnostic point of view, MSA should always be suspected in the hypokinetic patient with little response to levodopa who also manifests prominent autonomic or cerebellar dysfunction.
   b. **Neuroimaging.** MRI of the brain shows putaminal hypointensity in SND, probably because of excessive iron deposition in this structure. Cerebellar atrophy can be seen in OPCA.
   c. **Neuropathology.** Common to all the MSA syndromes is the presence of characteristic glial cytoplasmic inclusions. Like Lewy's bodies seen in IPD, these inclusions

stain for the protein alpha-synuclein. Especially in SDS, additional neuronal loss and gliosis are seen in the structures responsible for autonomic functions such as the intermediolateral cell column of the spinal cord and the dorsal motor nucleus of the vagus.

4. **Dementia syndromes.** AD, Pick's disease, and DLB are degenerative CNS disorders whose predominant manifestation is dementia. Familial frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) are associated with mutations in the tau gene. Although the degenerative process in these disorders has a predilection for certain cortical regions, subcortical structures may also be involved leading to extrapyramidal manifestations including parkinsonism. The key to identifying a primary dementing disorder as a cause of parkinsonism is the early appearance of dementia, often antedating the onset of parkinsonism (e.g., dementia occurs before or within one year after the onset of parkinsonism in DLB).

D. Heredodegenerative diseases.

1. **Wilson's disease.** An autosomal recessive condition associated with impairment of copper excretion caused by a genetic defect in a copper transporting ATPase, resulting in copper accumulation in different organ systems including the CNS, liver (cirrhosis), cornea (Kayser–Fleischer's ring), heart, and kidney.
   a. **Clinical.** The age of presentation ranges from 5 to 50, peaking between 8 and 16. Neurologic symptoms are present at the onset of the disease in about 40% of patients. Extrapyramidal symptoms such as dystonia, rigidity, and bradykinesia are more common in children, whereas tremor and dysarthria are more likely to appear in adults. A variety of psychiatric symptoms can be seen in Wilson's disease. An especially important clue to the diagnosis is the presence of liver dysfunction such as cirrhosis or chronic active hepatitis, especially in a young patient. The combination of bradykinesia and tremor in these patients may suggest PD, but the very young age of onset, and the presence of psychiatric symptoms, liver dysfunction, or dystonia should prompt a search for laboratory signs of Wilson's disease. As the consequences of Wilson's disease are preventable and the neurologic symptoms are reversible with early treatment using copper chelating drugs, this condition should always be kept in the differential diagnosis of atypical parkinsonism, especially that appearing below the age of 50.
   b. **Neuroimaging.** MRI of the brain shows ventricular dilation as well as cortical and brainstem atrophy. The basal ganglia, especially the putamen, may appear either hypo- or hyperintense on T2 weighted studies, and hypodense on CT examinations. Occasionally, there is the characteristic "face of the giant panda" appearance of the midbrain on MRI studies.
   c. **Neuropathology.** There is generalized brain atrophy. The putamen, globus pallidus, and caudate nucleus are cavitated and display a brownish pigmentation reflecting copper deposition.
   d. **Other tests.** Plasma ceruloplasmin is the most useful screening test and is usually below 20 mg per dl (normal: 25 to 45 mg per dl). Plasma copper is decreased and 24-hour urinary copper excretion is increased. Slit lamp examination of the cornea reveals Kayser–Fleischer's ring in almost all neurologically symptomatic patients and represents a very specific but not pathognomonic finding. If one or more of these tests are normal and the diagnosis is in doubt, it should be confirmed by liver biopsy that shows increased copper content. Because of abundance of disease-specific mutations and their location at multiple sites across the genome, genetic diagnosis is limited to kindreds of known patients.
2. **HD.** A relentlessly progressive autosomal-dominant disorder characterized by dementia, psychiatric disturbance, and a variety of movement disorders.
   a. **Clinical.** The major clinical components of HD are cognitive decline, various psychiatric abnormalities (personality changes, depression, mania, and psychosis), and movement disorder. Although chorea is the most common motoric symptom, bradykinesia usually coexists with chorea and may explain the occasional exacerbation of the motor impairment when control of the chorea is attempted with antidopaminergic medications. An abnormality of saccadic eye movement, particularly slow saccades, is often one of the earliest neurologic signs of this disorder. The typical age of onset is in the fourth or fifth decade, but 10% of the patients develop symptoms

before age 20 (juvenile Huntington's). Successive generations may develop symptoms at a progressively earlier age, especially if they have inherited the disease from their father, reflecting the genetic phenomenon of anticipation. The juvenile form presents with a combination of a progressive akinetic-rigid syndrome (Westphal's variant), dementia, ataxia, and seizures. It is these akinetic-rigid patients that are most likely to be confused with IPD, but the autosomal-dominant inheritance pattern, the early age of onset, and the presence of seizures should suggest the correct diagnosis. The duration of illness from onset to death is about 15 years for adult onset HD and 8 to 10 years for those with onset in childhood.

b. **Neuroimaging.** Atrophy of the head of the caudate is the principal finding on neuroimaging. It can be appreciated on either MRI or CT scan.

c. **Neuropathology.** There is loss of medium spiny striatal neurons, as well as gliosis in cortex and striatum (particularly the caudate). This striatal neuronal loss accounts for the drastic decrease in the two neurotransmitters associated with these cells, GABA, and enkephalin.

d. **Other tests.** HD can be diagnosed and presymptomatic individuals can be identified with great certainty using DNA testing. The genetic abnormality has been localized to chromosome 4 and consists of an expansion of the usual number of repeats of the trinucleotide sequence CAG. The presence of 40 or more CAG repeats confirms the diagnosis of HD. Reduced penetrance is seen with 36 to 39 CAG repeats. Because of the ethical, legal, and psychological implications of presymptomatic predictive testing, it should only be carried out by a team of clinicians and geneticists fully sensitive to these issues and aware of published guidelines.

3. **Other neurologic conditions**, occasionally associated with parkinsonism, include neuroacanthocytosis, neurodegeneration with brain iron accumulation (NBIA, formerly known as Hallervorden–Spatz's syndrome), Machado–Joseph's disease (spinocerebellar ataxia type 3), Fragile X-associated tremor/ataxia syndrome (FXTAS), and familial calcification of the basal ganglia.

V. DIAGNOSTIC APPROACH

A. Clinical. Careful history taking and physical examination are essential. A meticulous survey of the past medical and psychiatric history, family history, and occupational or environmental exposure to toxins will reveal most causes of secondary parkinsonism. Disease onset at a young age, a strong family history of the same disorder, lack of resting tremor, absent response to levodopa and early appearance of postural instability, gait disorder, dysautonomia, or dementia should be considered red flags in the history suggesting a diagnosis other than IPD. The general physical examination is important because it may reveal signs of a systemic disease that is contributing to secondary parkinsonism. Neurologic examination establishes whether parkinsonism is isolated or associated with involvement of other neuronal systems in the CNS. The presence of aphasia, apraxia, supranuclear gaze palsy, cortical sensory loss, alien limb phenomenon, pyramidal signs, lower-motor neuron findings, myoclonus, chorea, or dystonia indicate more widespread CNS involvement than is the case in IPD.

B. General laboratory tests.

1. CBC and peripheral blood smear. Acanthocytes are found on a fresh peripheral blood smear in neuroacanthocytosis. A low-hemoglobin level and elevated reticulocyte count consistent with hemolytic anemia may be present in Wilson's disease.
2. Blood chemistry. Abnormal liver function tests may be found in Wilson's disease. Hypocalcemia, hypomagnesemia, and a low-parathormone level are present in hypoparathyroidism. Elevated CK is associated with neuroacanthocytosis, and elevated serum lactate, suggesting lactic acidosis, is found in mitochondrial cytopathies. Low-thyroxin and high-TSH levels point to hypothyroidism.
3. Serology. Elevated ESR, C-reactive protein, or rheumatoid factor may be found in inflammatory or rheumatologic conditions. Antibodies against glutamic acid decarboxylase are present in stiff person syndrome.

C. Radiology.

1. Plain X-rays. Spine X-rays may reveal ankylosing spondylitis or osteoarthritis as the cause of mechanical limitation of movement.
2. CT or MRI of the brain. CT may demonstrate a neoplasm, stroke, hydrocephalus, basal ganglia calcification, atrophy, or sequelae of trauma. It has some limitations, in that the resolution is not always adequate to evaluate density changes or storage materials in the basal ganglia, and brainstem or cerebellar cuts may suffer from bone artifact (see Chapter 32). In these circumstances, an MRI of the brain is more desirable. Several characteristic MRI patterns that are suggestive of specific hypokinetic disorders are listed below:
   a. Many lacunar strokes: vascular parkinsonism.
   b. Large ventricles, out of proportion to cerebral atrophy; transependymal flow: NPH.
   c. Caudate atrophy: HD.
   d. Decreased T2 signal in striatum: MSA.
   e. Homogeneous decreased T2 signal or decreased T2 signal with a central hyperintensity (Tiger's eye) in the globus pallidus: NBIA.
   f. Striatal necrosis: Wilson's disease, Leigh's disease, and CO intoxication.
   g. Midbrain atrophy: PSP.
   h. Asymmetric frontoparietal atrophy: CBGD.
3. PET or SPECT. With modern analysis techniques, fluorodeoxyglucose PET, by characterizing the regional cerebral metabolism pattern, can distinguish PD, MSA, and PSP from one another with >90% accuracy. These techniques are not readily available at many hospitals, however. The status of nigral dopaminergic neurons can be determined using fluorodopa PET or [I^{123}]FP-CIT(Ioflupane) SPECT. In IPD, either of these two modalities demonstrates a loss of dopaminergic nigral cells. Although both of these techniques identify nigral dopaminergic dysfunction, they do not clearly differentiate between IPD and other causes of parkinsonism such as MSA, PSP, and CBD. The major clinical usefulness of Ioflupane SPECT is that it is very accurate in distinguishing IPD from mimicing conditions that do not involve dopamine producing cells such as ET, dystonic tremor or drug-induced parkinsonism. Of additional importance, SPECT imaging equipment is available at many hospitals.

D. Electrophysiology.

1. ECG. Heart block may be present in mitochondrial cytopathy.
2. EEG. Epileptic activity or focal slowing may appear with focal lesions (stroke and tumor). Slow background activity is seen in some primary dementias. Periodic triphasic complexes may be present in CJD (see Chapter 33).
3. EMG/nerve conduction studies: Mild nerve conduction slowing suggestive of axonal polyneuropathy is seen in neuroacanthocytosis. Myopathic findings on EMG (see Chapter 33) may be present in cases of mitochondrial cytopathies.

E. Neuropsychological testing. If there is clinical suspicion of dementia, formal testing should be employed to plot the profile of cognitive decline (see Chapter 4).

F. CSF analysis. Elevated protein and pleocytosis can be detected in CNS infections. The presence of high levels of the 14-3-3 protein in CSF is highly suggestive of CJD (see Chapter 33). A large volume of CSF can be removed (Fisher's test) with observation for improvement in neurologic signs as one means of corroborating the diagnosis of NPH.

G. Special diagnostic tests.

1. Wilson's disease. Low ceruloplasmin, low serum copper, increased 24-hour urinary copper excretion, and Kayser–Fleischer's ring on slit lamp examination of the cornea are all suggestive of Wilson's disease. Liver biopsy for copper content is performed only if the diagnosis is in question.
2. NPH. Intracranial pressure monitoring shows episodic appearance of high-pressure waves.
3. Genetic testing. Monogenic PD is found in approximately 3% of IPD patients and mutations in these PD genes are most common in those with an early age of onset or those belonging to certain ethnic groups. Commercial testing is available for LRRK2, PINK1, DJ-1, SNCA (alpha-synuclein), GBA (glucocerebrosidase), and Parkin genes. In patients with onset before age 51, almost 20% have a mutation in one of these genes, most commonly Parkin, followed by LRRK2. The mutation rate is still higher for

those with onset prior to age 30. In individuals developing PD under the age of 20, as many as 77% have a mutation of the Parkin gene. Jewish PD patients are more likely to harbor a mutation of the GBA gene. Although genetic testing does not affect patient management, it can clarify prognosis and allow genetic counseling. Genetic testing is also increasingly more available for other conditions where parkinsonism can be a clinical component of the overall syndrome such as HD, FXTAS, SCA 3, and other SCA subtypes, dystonia subtypes, and various mitochondrial conditions.

VI. WHEN TO REFER

Patients with new onset hypokinesia who have the following characteristics are less likely to have IPD and would benefit from referral to a movement disorders specialist:

A. Early onset, for example, before 50 years of age.
B. Early gait difficulty and postural instability.
C. Prominent dementia.
D. A family history of parkinsonism.
E. Supranuclear gaze palsy.
F. Apraxia, alien limb phenomenon, cortical sensory loss, myoclonus, marked asymmetry of neurologic involvement.
G. Bulbar, cerebellar, or pyramidal dysfunction.
H. Marked dysautonomia.
I. Absent, limited or unsustained response to levodopa.

Recommended Readings

Clarke CE. Parkinson's disease. *BMJ*. 2007;335(7617):441–445.

de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006;5(6):525–535.

Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med*. 2004;351(24):2498–2508.

Klein C, Djarmati A. Parkinson disease: genetic testing in Parkinson disease-who should be assessed? *Nat Rev Neurol*. 2011;7(1):7–9.

Poewe W, Mahlknecht P. The clinical progression of Parkinson's disease. *Parkinsonism Relat Disord*. 2009;15(4): S28–S32.

Uc EY, Rizzo M, Anderson SW, et al. Visual dysfunction in Parkinson disease without dementia. *Neurology*. 2005;65(12):1907–1913.

CHAPTER 30

Approach to the Patient with Acute Muscle Weakness

Holli A. Horak

Muscular weakness implies lack or diminution of muscle strength, which leads to an inability to perform the usual function of a given muscle or group of muscles. Muscle weakness should be differentiated from fatigue, which is the subjective perception of being "weak." In other words, weakness is the objective evidence of lack of strength, and fatigue is a subjective symptom. After the existence of "true" weakness is established, an etiologic search should be conducted. Muscular weakness has diverse causes. This chapter emphasizes the diagnostic evaluation and differential diagnosis of the leading neurologic causes of acute weakness involving the peripheral nervous system (PNS).

I. EVALUATION

A. History. Determine the onset, course, and distribution of weakness and any associated neurologic findings (such as cranial nerve involvement). Ask if there is a history of recent febrile illness, change of medications, or exposure to toxic agents. Ask the patient if he/she has had prior episodes of weakness or if there is a family history of muscle disease.

B. General physical examination. Examine the skin for evidence of connective tissue disease or dermatomyositis-associated skin changes (Gottron's papules, heliotrope rash). Evaluate the patient for thyroid enlargement, proptosis, or tachyarrhythmia to assess for any evidence of hyperthyroidism. Evaluate the respiratory system, including neuromuscular parameters such as cough, ability to count up to 30 during exhalation, or, more objectively, bedside forced vital capacity (FVC) and negative inspiratory force (NIF).

C. Neurologic examination. The neurologic examination focusing on the PNS is highlighted.

1. **Distribution of weakness.**
   a. **Proximal symmetric muscle weakness** is usually found among patients with primary muscle disease such as polymyositis or dermatomyositis (PM/DM) or occasionally in patients with acute polyradiculoneuropathy, such as the Guillain–Barré's syndrome (GBS).
   b. **Proximal asymmetric muscle weakness** occurs among patients with nerve root trauma or acute brachial or lumbosacral plexopathies.
   c. **Distal symmetric muscle weakness** is rarely acute but may be seen with GBS or a subacute onset of chronic inflammatory demyelinating polyneuropathy (CIDP).
   d. Predominantly **distal asymmetric muscle weakness** occurs in patients with acute mononeuropathy such as foot-drop secondary to peroneal nerve palsy or wrist-drop resulting from radial nerve palsy. Mononeuritis multiplex (vasculitis of the PNS) manifests as a multifocal asymmetric peripheral weakness. Focal weakness also occurs with anterior horn cell involvement such as acute anterior poliomyelitis.
   e. **Acute diffuse muscle weakness** is found among patients with GBS, myasthenia gravis (MG), periodic paralysis, or tick paralysis.
2. **Muscle bulk.** Decreased muscle bulk is more often present in patients with chronic neuromuscular disease, such as muscular dystrophy, motor neuron disease (MND), or chronic neuropathy. Muscle bulk is usually normal during the acute stage of PM, MG, or acute demyelinating polyneuropathy (such as GBS).
3. **Muscle tone** often is normal in patients with muscle or neuromuscular junction diseases such as PM or MG. Tone is decreased (flaccid) in disorders of nerve function such as MND and GBS.

4. **Key muscles.** Examination of certain muscles can aid in narrowing the differential. For example, neck flexor and hip flexor muscles are compromised early in MG and PM.
5. **Sensory features.** Sensory symptoms occur among patients with polyneuropathy (GBS) or plexopathy. Sensory examination is normal among patients with primary muscle disease, MND or neuromuscular junction disease.
6. **Muscle stretch reflexes** are normal in patients with neuromuscular junction disease or primary muscle disease and are diminished or absent in patients with acute polyneuropathies such as GBS.

II. DIFFERENTIAL DIAGNOSIS

A useful approach in the evaluation of acute muscle weakness is to localize the site of lesion along the "motor unit," which consists of all the muscle fibers innervated by a single anterior horn cell. This discussion is limited to the most frequent conditions causing acute muscle weakness, particularly those leading to generalized muscle weakness.

A. Acute anterior horn cell disease.

1. **Acute anterior poliomyelitis** does not occur in the United States but can be seen in endemic areas in other countries. It typically follows a prodrome of systemic symptoms such as fever, nausea, vomiting, constipation, muscle pain, and headaches. Muscle weakness develops a few days after the prodromal stage with asymmetric weakness.
2. **The West Nile virus (WNV)** is associated with many disorders of the neurologic system. One of the neurologic manifestations of West Nile virus infection is an acute anterior horn cell myelitis. Rarely (0.1%), patients infected with WNV will develop acute flaccid paralysis in a focal or segmental distribution. Electromyography/nerve conduction studies (EMG/NCS) reveals evidence for MND and CSF analysis reveals a pleocytosis, elevated protein, and elevated IgM West Nile titers. The prognosis is poor.

B. Acute polyradiculoneuropathy.

1. **GBS** is an acute inflammatory demyelinating polyradiculoneuropathy (AIDP). It begins with lower-extremity paresthesia followed by ascending symmetric muscle weakness. Proximal muscles weakness may be more prominent in rare cases.

   Muscle stretch reflexes are universally absent or diminished. Bifacial peripheral-type weakness is frequent. Labile blood pressure, tachycardia, and other autonomic disturbances may occur as a result of involvement of the autonomic nervous system. Early in the course of the disease, the only EMG abnormality may be the absence of F waves as a result of proximal root involvement; later, the EMG shows changes consistent with demyelination. CSF examination shows elevation of protein with minimal or no pleocytosis.
2. **HIV infection.** Acute inflammatory demyelinating polyneuropathy similar to GBS can occur in patients with HIV infection. CSF pleocytosis is common.
3. **Cauda equina syndrome.** This is an acute polyradiculoneuropathy of the conus medullaris and lumbosacral nerve roots. Cauda equina syndrome manifests as lower extremity neuropathic pain, sensory disturbance, bowel and bladder dysfunction, and asymmetric BLE weakness. There are many causes, including neoplastic invasion, cytomegalovirus infection, and acute compression, such as from an epidural hematoma. Evaluation includes emergent imaging by MRI, often followed by lumbar puncture to evaluate the CSF.

C. Acute plexopathy.

1. **Acute idiopathic brachial plexopathy** is an uncommon disorder characterized by shoulder pain followed by weakness of shoulder girdle muscles, although distal arm muscles can be involved as well. Pain is a very important part of this syndrome. There are familial (hereditary) and sporadic cases. A history of a preceding febrile illness resulting from viral infection or vaccination is common. The diagnosis is made by clinical presentation and EMG.
2. **Acute lumbosacral plexopathy,** also known as diabetic amyotrophy or acute femoral neuropathy, is an acute inflammatory lesion of the lumbosacral plexus. Patients have weakness, sensory changes, and severe neuropathic pain, which can be asymmetric, due to unequal involvement of the various roots within the plexus. It sometimes occurs in

the setting of poorly controlled diabetes, but it can be a sign of carcinomatous infiltration or vasculitis and may be idiopathic. Diagnosis is made with clinical examination, EMG, and lumbar puncture.

3. **Other acute forms of plexopathy.** Acute plexus lesions can occur in patients who have sustained closed or open trauma to the brachial plexus, as in traction injuries. Neoplastic involvement, radiation, and orthopedic procedures also can cause plexus damage. Traumatic plexus injuries may follow gunshot wounds, needle punctures, and insertion of intravenous lines.

D. Acute neuropathy.

1. **GBS.** See III.B.
2. **Lyme's disease.** Acute demyelinating polyneuropathy can occur among patients with Lyme's disease. Lyme's disease can manifest with peripheral facial palsy and an ascending-type paralysis from the lower extremities, such as inpatients with GBS. CSF is abnormal, showing elevation of protein; but unlike GBS, there is a moderate degree of lymphocytic pleocytosis.
3. **Mononeuritis multiplex.** An asymmetric form of acute sensorimotor polyneuropathy is common among patients with vasculitis. EMG shows evidence of multiple mononeuropathies. The diagnosis is established by clinical presentation, EMG, nerve biopsy, and appropriate laboratory evaluation for vasculitis, including HIV and hepatitis C.
4. **Acute motor axonal neuropathy (AMAN)** was first recognized in northern China and was referred to as the *Chinese paralytic syndrome*. This condition has many similarities to GBS. Pathologically, it is an axonopathy without demyelination. CSF examination shows few cells but an increased protein level. Patients have flaccid, symmetric paralysis and areflexia. The clinical course usually is rapidly progressive and often causes respiratory failure. EMG shows decreased compound motor action potentials, consistent with a motor axonopathy. Latencies and F-waves are normal. Sensory nerve action potentials are within normal ranges. Rare variants include acute motor and sensory neuropathy, which includes sensory involvement.
5. **Acute intermittent porphyria (AIP).** Weakness usually starts in the proximal upper extremities, but all muscles may become involved. Muscle tone is reduced. There is areflexia or hyporeflexia, except for ankle jerks, which may be preserved. Weakness of bulbar muscles is uncommon. Paresthesia and autonomic dysfunction are frequently present. Attacks of AIP are usually associated with abdominal pain and cramping. During attacks of AIP, there are increases in urinary excretion of both Δ-aminolevulinic acid and porphobilinogen (PBG). The increase in PBG excretion (in milligrams per gram of creatinine) is greater than the increase in aminolevulinic acid excretion. The reverse is true in other forms of porphyria. NCSs show reduced amplitudes in motor and sensory nerves. Needle examination shows evidence of denervation consistent with axonal neuropathy.
6. **Acute critical illness neuropathy** often manifests in the intensive care unit as failure to wean from the ventilator. The patient has weakness and atrophy with amplitude loss on EMG and NCSs. Overlap with acute quadriplegic myopathy may be present (see Section II.F.5.).

E. Acute neuromuscular junction disorders.

1. **Presynaptic disorders.** Only selective disorders are considered. Lambert–Eaton's myasthenic syndrome, which has a more insidious presentation, is not discussed (see Chapter 48).
   a. **Botulism** is caused by ingestion of toxins produced by *Clostridium botulinum*. This disease often manifests as weakness of extraocular muscles followed by dysarthria, limb, and respiratory muscle weakness. This diagnosis is suggested by a history of ingestion of contaminated food. Repetitive nerve stimulation at high frequency (50 Hz) will show an incremental response. Botulism intoxication is seen among infants, whose gastrointestinal tract can be colonized by *C. botulinum*.
   b. **Tick paralysis** is a rare disease caused by the female tick *Dermacentor andersoni*. Neurologic symptoms begin with walking difficulty and imbalance followed by ascending flaccid paralysis and are flexia. Ocular and bulbar muscles may be involved. EMG shows reduced amplitude of muscle action potentials and an incremental

response to high-frequency stimulation, particularly during the acute stage. Removal of the tick may dramatically improve the weakness.

c. **Organophosphate poisoning** causes muscle weakness. Extraocular and bulbar muscles may be involved. Muscarinic symptoms such as miosis, increased salivation, and generalized fasciculations are often present. EMG findings usually are normal. Repetitive nerve stimulation may show incremental responses at high-frequency stimulation.

d. **Drug-induced** MG. Certain medications adversely affect neuromuscular transmission. Weakness usually involves proximal limb muscles rather than ocular or bulbar muscles. Drug-induced MG may be associated with the use of kanamycin, gentamicin, procainamide, primidone, or hydantoins.

2. **Postsynaptic disorders: MG.** Adult onset autoimmune acquired MG begins with fluctuating weakness; proximal muscle weakness is the presenting symptom in generalized myasthenia. Ocular myasthenia will often present with asymmetric ptosis and diplopia. Eventually, dysarthria, dysphagia, and respiratory distress may occur. There is fatigability induced by repetitive exercise. Muscle tone, bulk, reflexes, and sensory examination are normal. Diagnosis is based on clinical examination, single-fiber EMG or repetitive nerve stimulation, and laboratory assessment for acetylcholine receptor antibodies (AchR Ab). AchR binding antibodies are the most sensitive; blocking and modulating antibodies do not significantly increase the sensitivity. MuSK antibody MG occurs more often in females, with oculobulbar onset.

F. **Primary myopathy.**

1. **PM/DM.** Acute inflammatory myopathy usually begins with proximal symmetric weakness involving the muscles of the shoulder and hip girdle. Muscle tone, bulk, and muscle stretch reflexes are normal. There are no sensory deficits. PM is usually painless. Consider DM if typical skin lesions are present (erythematous rash in the periorbital, malar, forehead, or chest region, and a scaly, erythematous rash over the knuckles and extensor surfaces). Serum creatine kinase (CK), aldolase, lactic acid dehydrogenase, and aspartate aminotransferase levels often are elevated. Erythrocyte sedimentation rate (ESR) may be increased. NCS and amplitude are normal. Needle examination of the muscles shows increased spontaneous potentials, such as fibrillations and positive sharp waves. With activation, there is increased recruitment of polyphasic, short-duration, low-amplitude voluntary motor unit potentials. Muscle biopsy shows an inflammatory response, which differs depending on the pathologic process present: perimysial inflammation is noted in DM and intrafascicular inflammation is present in PM. The biopsy will also show muscle fiber necrosis and a variable degree of muscle fiber regeneration.
2. **Acute infectious myositis.** Postviral myositis is associated with myalgia and weakness, which may be severe. HIV infection can manifest as proximal muscle weakness.
3. **Acute toxic myopathy.** Most drug-induced myopathies are subacute in onset. Amiodarone can cause acute myopathy and paralysis. Hyperthyroidism can cause acute weakness in severe cases.
4. **Acute periodic paralysis** is a group of primary muscle diseases associated with acute transient quadriparesis without respiratory compromise. Patients may have had attacks for years but will present to the emergency room for a particularly severe attack. The episodes of quadriparesis typically resolve spontaneously, although, over the years, patients may develop a chronic myopathy. These diseases are also known as channelopathies because the etiology is a defect in an ion pore of the muscle membrane. Hyperkalemic periodic paralysis (Hyper PP) is caused by a defect in the gene coding for a muscle sodium channel (SCN4A) and hypokalemic periodic paralysis (Hypo PP) is caused by either a gene defect in a Calcium-channel of the muscle (CACNA1S) or the sodium SCN4A channel. There is significant overlap between the presentations of both conditions and diagnosis is best confirmed by genetic testing. Patients with hyperkalemic periodic paralysis may have clinical myotonia. The diagnosis is suspected if the patient has a history of intermittent weakness induced by exertion or a high-carbohydrate diet, a family history, and abnormal serum potassium levels during attacks. EMG may be normal or may show decreased CMAPs; the prolonged exercise test can be used to

demonstrate a reduction in CMAP amplitude. Muscle biopsy may show a vacuolar myopathy.

5. **Acute steroid quadriplegic myopathy** occurs in the ICU setting. Patients will have flaccid paralysis and difficulty weaning from the ventilator. Sometimes, this disease is associated with treatment for status asthmaticus using high-dose steroids and neuromuscular blockade agents. The EMG shows either myopathic features or an electrically silent muscle; it is differentiated from ICU Neuropathy by normal sensory NCS. Muscle biopsy typically shows loss of myosin filaments at electron microscopic examination.

III. LABORATORY STUDIES

A. Blood tests. If myositis is suspected, measurement of serum CK, ESR, lactic acid dehydrogenase, and aspartate aminotransferase are useful. Anti-Jo antibody test results are positive in approximately 30% of cases of PM. The presence of this antibody is a marker of risk for pulmonary fibrosis. Other autoantibodies associated with inflammatory myopathy are insensitive and not diagnostically useful.

If vasculitis is suspected, measure ESR, serum complement, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and cryoglobulins. Consider evaluating the patient for HIV and chronic hepatitis infection.

If MG is suspected, check acetylcholine receptor antibody (binding) titers and thyroid function tests. If these results are negative, consider testing MuSK antibodies and antibodies to the voltage-gated calcium channel (Table 30.1).

In conditions such as periodic paralysis, serum potassium, and thyroid function tests may or may not be helpful. Potassium (K^+) levels can fluctuate greatly during the course of an attack. The genetic defects for some channelopathies are known. Commercial testing is available for the genes encoding for the SCN4A channel (hyperkalemic periodic paralysis/paramyotonia congenital and hypokalemic periodic paralysis, type 2) and the CACNA1S channel (hypokalemic periodic paralysis, type 1).

Autoantibodies are associated with a variety of peripheral neuropathy syndromes, a few of which can present acutely. Anti-GM1 ganglioside antibody can be seen with the GBS variant, AMAN. Patients affected with AMAN may have had a recent *Campylobacter jejuni* infection. The anti-GQ1b ganglioside antibody is both sensitive and specific for the Miller-Fisher variant of GBS. This variant manifests as ophthalmoparesis, ataxia, and areflexia.

In suspected cases of West Nile viral infection, acute and convalescent titers should be drawn (serum IgG and IgM levels).

B. Lumbar puncture is indicated in the evaluation of patients with suspected GBS, in which CSF may show protein elevation with minimal or absent pleocytosis (albuminocytologic dissociation). In patients with an acute poliomyelitis picture (acute MND), the lumbar puncture may show lymphocytic pleocytosis and protein elevation. Check for WNV-IgG antibodies, and, if the patient is immunocompromised (ICP), check the CSF for herpes (HSV), varicella (VZV), and CMV infections as well.

C. Electrodiagnostic studies. EMG and NCS are extremely useful in the evaluation of disorders of motor neurons, peripheral nerves, neuromuscular junctions, and muscles. The value of electrodiagnostic tests is discussed in Chapter 33.

D. Muscle biopsy. Muscle tissue can be obtained by means of open incision. The site of muscle biopsy should involve a weak but not atrophic muscle. Specimen handling and interpretation of muscle biopsy findings by an experienced pathologist are crucial. Muscle biopsy aids in diagnosis of acute primary muscle pathologies such as PM/DM.

E. Nerve biopsy is most often performed on the sural nerve. This procedure should be performed only when the biopsy results will influence management. One of the leading indications for nerve biopsy is the suspicion of vasculitis (mononeuritis multiplex).

F. MRI of the affected muscles may indicate inflammation in an infectious/inflammatory myositis. Atrophy of the muscles will be noted in subacute to chronic processes, such as dystrophy or MND.

TABLE 30.1 Diagnostic Table for Selected Diseases Causing Acute Muscle Weakness

	GBS	MG	PM/DM
Features			
Initial weakness	Typically distal	Ocular and bulbar	Proximal
Fatigability with repeated testing	Not present	Prominent	Not present
Wasting/atrophy	Not in acute phase	Not typically present	Can occur late in disease
Sensory loss	Present	Not present	Not present
Reflexes	Diminished/absent	Normal	Normal
Fasciculations	Not typically noted	Rarely present in severe disease	Not present
CSF protein	Elevated	Normal	Normal
EMG			
Fibrillations	Occur late in disease	Occur with long standing disease	Present
Fasciculations	Can be present	Occur with long- standing disease	Not present
Motor unit recruitment	Marked decrease	Variable	Increased
CK	Normal	Normal	Increased
AchR Ab	Negative	Elevated	Negative
Muscle biopsy	Not indicated	Not indicated	Inflammation

IV. DIAGNOSTIC APPROACH

Diagnosis begins with establishing the presence of weakness and then determining whether the weakness reflects upper or lower motor neuron involvement. After exclusion of upper motor neuron weakness, further localization within the motor unit is needed. Diagnosis often requires support by laboratory studies. Of these, the most confirmatory and cost-effective test is EMG. Muscle biopsy is recommended for evaluation of PM/DM. Nerve biopsy is indicated mainly in cases of suspected vasculitic neuropathy.

V. MANAGEMENT

Patients with acute onset of generalized neuromuscular weakness need to be hospitalized, particularly those with acute paralysis or paresis. If respiratory or bulbar muscles are compromised, patients need admission to an intensive care unit. Bedside pulmonary function tests (FVC and NIF), are used to monitor respiratory function. A sustained drop in FVC, or an FVC <1 L, indicates impending respiratory failure, and intubation is indicated. Neuromuscular diseases with a subacute onset may sometimes be managed in the outpatient setting. Many of the therapies for neuromuscular weakness require careful monitoring and follow-up assessment, especially if steroids and immunosuppressive agents are used.

Recommended Readings

Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain–Barré syndrome. *Ann Neurol*. 1990;27(suppl):S21–S24.

Dalakas MC. Therapeutic approaches in patients with inflammatory myopathies. *Semin Neurol*. 2003;23(2):199–206.

Davis LE, DeBiasi R, Goade DE, et al. West Nile virus neuroinvasive disease. *Ann Neurol*. 2006;60:286–300.

Hirano M, Ott BR, Raps EC, et al. Acute quadriplegic myopathy: a complication of treatment with steroids, nondepolarizing blocking agents or both. *Neurology*. 1992;42:2082–2087.

Hughes JM, Blumenthal JR, Merson MH, et al. Clinical features of type A and B food-borne botulism. *Ann Intern Med*. 1981;95:442–445.

Keesey JC. Clinical evaluations and management of myasthenia gravis. *Muscle Nerve*. 2004;29:484–505.
Leger JM, Bouche P, Bolgert F, et al. The spectrum of polyneuropathies in patients infected with HIV. *J Neurol Neurosurg Psychiatry*. 1989;52:1369–1374.
Ridley A. The neuropathy of acute intermittent porphyria. *Q J Med*. 1969;38:307–333.
Wilbourn AJ. Plexopathies. *Neurol Clin*. 2007;25(1):139–171.

CHAPTER

31 Approach to the Patient with Neurogenic Orthostatic Hypotension, Sexual and Urinary Dysfunction, and Other Autonomic Disorders

Emilio Oribe and Bhuwan P. Garg

The autonomic nervous system (ANS) maintains internal homeostasis and regulates protective responses by continuously monitoring and responding to internal and external stimuli. This is achieved through autonomic reflex pathways and extensive vasomotor, visceromotor, and sensory innervation. The baroreflex, an example of an autonomic reflex, regulates blood pressure (BP), heart rate (HR), and extracellular fluid volume (Fig. 31.1).

ANS dysfunction may be focal or generalized depending on the site of a lesion in an autonomic reflex pathway. Central forms of ANS dysfunction are because of lesions involving neurons of the CNS, brainstem, spinal cord, and preganglionic neurons, whereas with peripheral forms, dysfunction is because of lesions involving peripheral ganglia and postganglionic neurons, or to lesions involving afferent autonomic reflex limbs (Fig. 31.1). Selected autonomic symptoms and findings are summarized in Table 31.1. Numerous diseases result in autonomic dysfunction (Table 31.2).

I. EVALUATION OF THE PATIENT WITH ANS SYMPTOMS

A. History. All patients presenting with autonomic dysfunction should undergo a **comprehensive medical and neurologic history and physical examination**. Important elements of the autonomic history include the following:

1. **Chief autonomic complaints**, with severity of symptoms, their distribution and frequency, progression, the presence of aggravating and alleviating factors, and a measure of the degree of disability are determined.
2. **Review of ANS systems** including cardiovascular, sexual, urinary, gastrointestinal, vasomotor, thermoregulatory and sudomotor, secretomotor, pupillomotor, and sleep functions.
3. **Medication review** (antihypertensive, psychotropic, antiandrogenic, laxative medications, and alcohol and recreational drugs can produce ANS dysfunction).
4. **Psychosocial evaluation** to determine the impact of ANS dysfunction on quality of life.
5. **Family history** (inherited autonomic disorders).

B. Physical examination. The physical and neurologic examination indicates the site and extent of the lesion responsible for ANS dysfunction and defines associated illness. A comprehensive examination includes supine and upright BP and HR, and examination of the skin and mucosa to assess sweating patterns and to determine if trophic lesions are present. A vascular system examination is important. In patients with **genitourinary and anorectal dysfunction** complaints (see the following list), the physical examination also includes the following:

1. Abdominal examination to determine if aortic dilatation is present (1% of patients with erectile dysfunction [ED] have abdominal aortic aneurysm) or masses are present.
2. Stretching and palpating the penis for an indication of the integrity of erectile tissue and if Peyronie's plaques (lumps within the penis) are present.
3. Testicular volume and consistency.
4. Cremasteric reflex (testicle retraction on stroking the thigh), anal wink reflex (anal sphincter contraction on stroking perianal skin), and bulbocavernosus reflex (anal sphincter contraction on squeezing the glans penis or clitoris).
5. Rectal examination to determine if prostatic hypertrophy, fecal impaction, and prolapse are present.

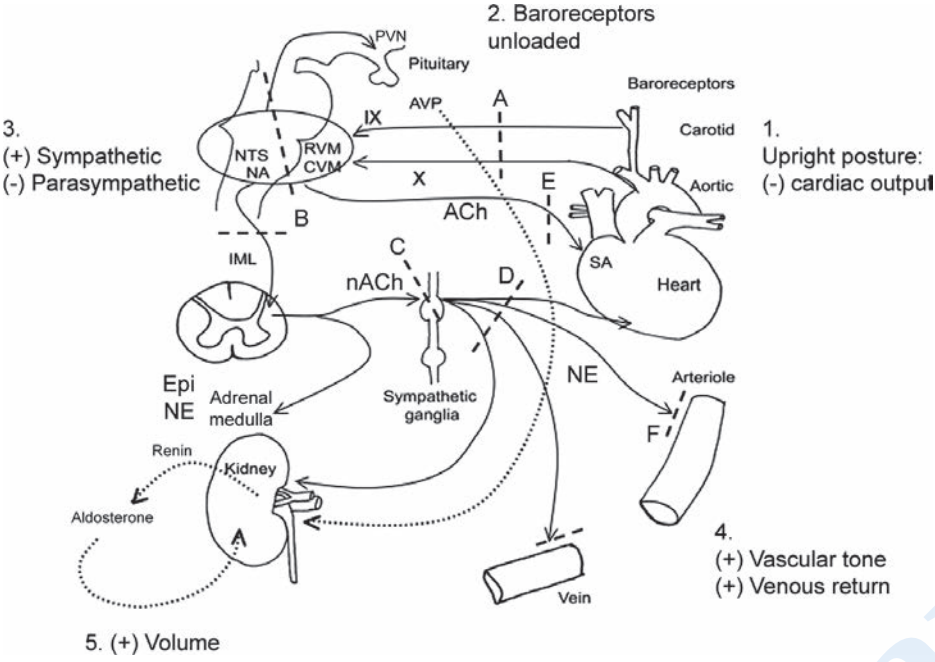

FIGURE 31.1 The baroreflex. 1. Standing produces "pooling" of 600–1,000 mL of blood to the lower body (mainly limb and splanchnic capacitance circulation), reducing venous return and cardiac output (by approximately 30%). 2. This is sensed by specialized stretch receptors (arterial and cardiopulmonary baroreceptors) that in turn activate (unload) baroreflexes. Inputs from carotid and aortic baroreceptors travel with the glossopharyngeal (IX) and vagus (X) nerves to converge on cardiovascular centers in the brainstem and medulla (mainly nucleus of the tractus solitarius) and their projections. 3. The physiologic baroreceptor reflex response to the volume shifts produced by upright posture is a compensatory increase in sympathetic tone with a decrease in parasympathetic outflow. 4. Sympathetic nerve terminals release NE that produces increased vasoconstriction of skeletal and mesenteric muscle vessels, HR, and cardiac contractility. Additional increases in venous return occur through a "pumping" effect of contracting limb and abdominal muscles engaged by the effort of standing (not shown).
5. A longer term response promoting extracellular fluid volume expansion includes baroreflex-mediated release of renin, angiotensin, and aldosterone, leading to increased renal Na^{++} absorption, and release of vasopressin, with an increase in free-water absorption.
A: Afferent baroreflex limb dysfunction is present when lesions involve baroreceptors and IX and X cranial nerves (neck surgery, radiotherapy, trauma, neuropathies, and autonomic disorders such as baroreflex failure, Holmes-Adie syndrome, and HSAN III). B: Central lesions involve the ventrolateral medulla (MSA), descending sympathetic pathways (medullary lesions, spinal cord lesions above T5), and IML (MSA, Lewy's body disorders).
C: Sympathetic ganglia lesions involve sympathetic ganglia (autoimmune ganglionopathies associated with nAChR antibodies or paraneoplastic, Lewy's body disorders).
D, E: Postganglionic sympathetic and efferent parasympathetic lesions are present with small fiber neuropathies (diabetes, amyloidosis, Sjögren's syndrome, HSAN III).
F: Efferent sympathetic neuroeffector junction dysfunction occurs with dopamine β-hydroxylase deficiency and α-1 adrenoceptor blocking drugs.
nAChR, nicotinic acetylcholine receptor antibodies; *AVP*, arginine vasopressin; *CVM*, caudal ventrolateral medulla; *Epi*, epinephrine; *HSAN III*, hereditary sensory autonomic neuropathy type III; *IML*, intermediolateral cell columns of the spinal cord; *NA*, nucleus ambiguus; NE: morepimephrime *NTS*, nucleus tractus solitarius; *RVM*, rostral ventrolateral medulla; *SA*, sinus node.

TABLE 31.1 Clinical Features of ANS Dysfunction

	Common Symptoms	Examination
Cardiovascular autonomic	Orthostatic intolerance: syncope, near-syncope, lightheadedness, confusion and impaired cognition, weakness, slurring, visual disturbances, tremors, neck and shoulder (coat hanger) aches	OH, hypotension, orthostatic tachycardia
	Exercise intolerance, silent myocardial infarction, intraoperative cardiovascular liability, increased mortality	Tachycardia, loss of HR respiratory sinus arrhythmia. Intraoperative hypothermia, reduced hypoxic-ventilatory drive
Vasomotor	Skin discoloration	Flushing, pallor, distal cyanosis, trophic changes. Changes in skin blood flow absent
Sudomotor and thermoregulatory	Hypohidrosis, hyperhidrosis, heat/cold intolerance	Abnormal temperature regulation, hypothermia, hyperthermia
Secretomotor	Dry mouth, excessive salivation, gustatory sweating, tearing, dry eyes	Dry mouth, dry eyes
Gastrointestinal	Difficulty swallowing, constipation, early satiety, bloating, nausea, vomiting, abdominal pain/cramping, diarrhea, fecal incontinence, weight loss	Abnormal bowel sounds, abdominal distention, reduced anal tone. Gastroparesis, esophageal enteropathy
Bladder	Incontinence, urgency, weak stream, dribbling, hesitancy, retention, recurrent infection	Distended bladder, increased postvoid residual
Sexual	Loss of libido, decreased genital engorgement, ED, ejaculatory dysfunction, dyspareunia	Decreased penile or clitoral and labial engorgement, decreased genital lubrication
Pupillomotor	Glare, blurred vision, poor night vision	Impaired pupillary responses

C. Autonomic testing. ANS testing is considered an extension of the physical examination. **The data from ANS testing is of most value when the selection of tests is guided by the clinical findings.** The goal of testing is to confirm the presence of autonomic dysfunction, determine the extent of autonomic involvement, and to localize the site of a lesion in the ANS reflex arc, and distinguish primary from secondary autonomic disorders. Most ANS tests assess the integrity of a reflex arc by recording stimulus-evoked effector organ responses. The more popular tests rely on measuring those effector organ responses that are easily recorded (i.e., changes in HR, BP, pupillary size, etc.). Common bedside tests are shown in Table 31.3. More sophisticated tests include beat-to-beat arterial pressure recordings during different challenges, and the measurement of sweat output (the quantitative sudomotor axon reflex test [QSART], measuring efferent sudomotor function). **Usually a battery of several tests is required to reach a diagnosis of autonomic dysfunction** (abnormal tests do not always imply disease).

1. **Screening tests.** Selection of testing is directed by the clinical presentation.
   a. Complete blood count and differential.
   b. Urinalysis and renal function studies.
   c. Hemoglobin A1C, fasting and postprandial glucose, and glucose tolerance test.
   d. TSH levels.
   e. HIV testing.
   f. Immunoelectrophoresis (serum and urine).
   g. Sweat gland nerve fiber density and epidermal nerve fiber density (skin biopsy).

TABLE 31.2 Selected Autonomic Disorders

	Autonomic Disorders
Central autonomic disorders	MSA
	PAF (peripheral involvement predominant), Parkinson's disease, DLB
	Disorders of different causes (cerebrovascular, epileptic, tumoral, demyelinating, traumatic, infectious, and degenerative) and autonomic presentations involving primarily: frontal lobes, limbic system, hypothalamus, brainstem, cerebellum, and spinal cord.
Autonomic neuropathies	a. Acute and subacute autonomic neuropathies: subacute autoimmune autonomic neuropathy (panautonomic neuropathy and pandysautonomia), subacute paraneoplastic autonomic neuropathy, Landry–Guillain–Barré's syndrome, botulism, porphyrias, drug induced and toxic autonomic neuropathies.
	b. Chronic peripheral autonomic neuropathies: distal small fiber neuropathies.
	Sympathetic and parasympathetic neuropathies: DAN, amyloidosis, autoimmune autonomic neuropathy (paraneoplastic and idiopathic), sensory neuronopathy with autonomic failure, hereditary neuropathies.
Catecholamine disorders	Baroreflex failure, tumors that secrete catecholamines (pheochromocytoma, neuroblastoma, chemodectoma, and familial paraganglioma syndrome), disorders affecting neurotransmitter metabolism (tetrahydrobiopterin deficiency, aminoacid decarboxylase deficiency, dopamine β hydroxylase deficiency and Menkes' disease, monoamine oxidase deficiency states, and dopamine metabolism disorders).
Orthostatic intolerance disorders	POTS
	Mitral valve prolapse dysautonomia
	Idiopathic hypovolemia
Paroxysmal syncope	Neurally mediated hypotension and bradycardia (vasovagal), situational syncope
Miscellaneous	Hyperhidrosis (generalized, focal), anhidrosis (CNS, peripheral nerve, and dermatologic)
	Horner syndrome, Holmes–Adie's syndrome, Ross' syndrome, and crocodile tears
	Hirschsprung's disease
	Brugada's syndrome

Abbreviation: DAN, diasetic autonomic meuropathy; DLB, dementia with Lewy bodies; PAF, pure autonomic Failure; POTS, postural tachycardia syndrome.

h. Aminolevulinic acid, porphobilinogen, and porphyrins (24 hour urine collection), erythrocyte porphobilinogen deaminase activity.
i. Genetic testing (inherited neuropathies).
j. Amyloid staining in fat aspirate, rectal or gingival biopsy.
k. [Norepinephrine] plasma (supine and standing)

D. Antibody testing. Should always be guided by the clinical presentation.

1. Antinuclear antibodies, rheumatoid factor, Anti-Ro/SS-A, and Anti-La/SS-B.
2. Other antibodies: Neuronal nicotinic acetylcholine receptor, P/Q-type calcium channel, and acetylcholine receptor.
   a. Paraneoplastic antibodies: Anti-Hu (ANNA-1); Purkinje-cell cytoplasmic antibodies type 2 (PCA-2); and collapsin response-mediator protein 5 (CRMP-5), voltage gated calcium channels (VGCC).

TABLE 31.3 Bedside Autonomic Tests

		Response		
Test	**Methods**	**Normal**	**Abnormal**	**Site of lesion**
Active standing (supine rest for >3 min, or until BP, HR stable followed by unaided standing)	BP and HR supine and standing after 3 min	↑ HR <30 beats/min	= HR*	Sympathetic efferents
		↓ SBP <30 mm Hg	↓↓ SBP	
	HRmax/HRmin during first 30 s of active standing (30:15 ratio)	>1.02	1.00	Vagal efferents
Deep breathing (6 breaths/min)	Maximum—minimum HR	>10 beats/min	<8 beats/min	Vagal efferents
	Maximum R-R in expiration/minimum (E/I ratio)	>1.10	<1.05	
Valsalva's maneuver (blow into a mouthpiece maintaining 40 mm Hg for 15 s)	Longest R-R after maneuver/shortest R-R	>1.15	<1.10	No rebound bradycardia in phase IV: vagal efferents No tachycardia in phase II: S efferents
Mental stress (independent of baroreflex afferents)	HR and BP 2 min into the stress of mental arithmetic (i.e., serial 7 subtractions for 2.5 min)	↑ HR >12	=	Sympathetic efferents
NE release in response to upright posture	Supine and upright plasma NE	↑	=	Sympathetic efferents

Autonomic tests are used to explore the integrity of whole or of portions of autonomic reflex arcs. Abbreviation: R-R, electrocardiographic R-R intervals.
Exaggerated increases in HR suggest hypovolemia, deconditioning, POTS. Bedside tests require a sphygmomanometer and ECG or EMG instruments (typical settings: low-frequency filter =1–5 Hz and high-frequency filters =500 Hz). Plasma NE determinations are available through commercial laboratories. Testing should be performed in a quiet, comfortable environment.

E. Electrophysiologic studies. Nerve conduction studies and EMG help define large fiber peripheral neuropathies. Sphincter and pelvic floor EMG is a specialized technique (useful when performed by experienced examiners) in detecting denervation potentials in selected muscles in lesions of the anterior horn cells in the spinal cord.

F. Imaging. MRI of the brain and spine is essential in CNS and spinal cord lesions. Pelvic imaging may be indicated in those in whom structural lesions are suspected.

Clinical Presentation of Autonomic Dysfunction

NEUROGENIC ORTHOSTATIC (POSTURAL) HYPOTENSION

Orthostatic hypotension (OH) is a frequent and disabling manifestation of autonomic disorders. It may be the initial sign (i.e., "tip of the iceberg") heralding the onset of primary and secondary autonomic disorders.

A. Diagnosis. BP measured with a sphygmomanometer and pulse rate recorded while supine for a few minutes of quiet rest (i.e., once BP values have stabilized), and after standing up for 3 minutes is sufficient to determine if OH is present and may help with its differential diagnosis (Table 31.4). **OH is defined as a sustained decrease in systolic pressure of at least 20 mm Hg (30 mm Hg in patients with supine hypertension) and of diastolic pressure of at least 10 mm Hg within 3 minutes of standing or head up tilt to at least 60 degrees on a tilt table.**

B. Pathophysiology. The autonomic responses to gravitational volume shifts are complex, and rely on intact baroreflexes (Fig. 31.1). **In neurogenic OH, a patient's ability to normally increase vascular tone in upright postures is impaired as a result of a failure to appropriately release norepinephrine (NE), the sympathetic postganglionic neurotransmitter innervating blood vessels.** This may be because of an impaired afferent baroreflex pathway or to impaired efferent sympathetic outflow at central or peripheral sites. In OH, the lesions are below the medullary circulation centers.

TABLE 31.4 BP and HR Responses to Active Standing

Cause	BP	HR	Comments
Neurogenic OH	↓ SBP >20, ↓ DBP >10 after 3 min of standing or 60 degree head-up tilt	=	Efferent S vasomotor and vagal dysfunction caused by autonomic failure. Supine hypertension is frequent
Initial OH (on standing)	↓ SBP >40, ↓ DBP >20 (symptomatic), within 15 s. Absent OH >3 min of standing	↑	Temporary cardiac output and vascular resistance mismatch on standing (only detected with beat-to-beat BP recordings). No ANS failure
Delayed OH	↓ SBP >20, ↓ DBP >10 beyond 3 min of standing or tilt table testing	=,↑	Efferent sympathetic vasomotor dysfunction (mild/early)
Postprandial hypotension	↓ SBP >20 after 3 min of standing 1 hr after meal intake	=,↑	Efferent sympathetic vasomotor dysfunction
Neurallymediated (vasovagal)	↓	↓(paradoxical in the setting of ↓ BP)	Reflex withdrawal of efferent S and enhanced efferent PS tone. Typically with autonomic activation (pallor, cold sweats, nausea, vomiting), followed by prompt recovery
POTS	=, ↑	↑(>30 beats / min)	Exaggerated efferent sympathetic response to upright posture
Volume depletion	↓	↑	Dehydration. Intact baroreflexes.
Drugs	↓, =,↑ (depending on the drug)		Drugs with vasomotor and/or chronotropic effects. Drugs that produce dehydration.
Orthostatic hypertension	↑(>20 SBP, ↑DBP not defined)	↓, =,↑	Excessive venous pooling with increased sympathetic and hormonal activation (proposed)

OH may be "uncovered" under certain conditions, such as volume depletion and with vasodilatation (in hot environments, with exercise, alcohol and medications). BP values may vary following a circadian pattern (lower in the early mornings), and orthostatic BP decreases are exacerbated by prolonged bed rest, physical deconditioning and with aging.
Abbreviations: DBP, diastolic BP; HTN, hypertension; POTS, postural orthostatic tachycardia; PS, parasympathetic; SBP, systolic BP; S, sympathetic.

TABLE 31.5 Non-Pharmacologic Treatment of OH

Objective	Intervention
Understand mechanisms of OH and recognize factors that trigger/worsen OH.	Avoid: abrupt standing, prolonged motionless standing, Valsalva-like maneuvers, hyperventilation, excessive exercise, hot environments, alcohol, large meals, high carbohydrate meals, and drugs with hypotensive effects.
Increase venous return and cardiac output acutely to counter symptomatic hypotension	Counter-maneuvers with "muscle pumping" effect: leg and arm crossing, muscle tensing, handgrip, squatting, sitting, lying down, and raising limbs.
	Mechanical compression of capacitance vessels of abdomen and lower limbs: muscle toning exercises, abdominal and thigh binders.
Expand plasma volume	Adequate water intake (2–2.5 L fluid/d), adequate salt intake (>8 g/d) with additional 4–6 g/d if symptomatic from OH and 24 hr urinary [Na^{++}] <170 mmol/L. (Goal: light urine color, low urine specific gravity).
	Exercise (as tolerated).
Enhance vasoconstriction	Activate osmopressor reflexes (vasoconstriction in response to acute hypo-osmolarity): ~500 mL water by mouth over ~5 min.
	Tilt training by standing 30 min leaning with low back against a wall and feet 15 cm away from the wall, once or twice a day (as tolerated).
Plasma and red cell volume expansion	Stimulate renin and vasopressin release: head up at night in reverse Trendelenburg position with head of bed elevated by 10°–20°, and out of bed while awake.

C. **Causes. Medications** (in particular antihypertensive and diuretic agents), **autonomic neuropathies, spinal cord lesions** above T4 or T5, brainstem and medulla lesions, and **multiple system atrophy (MSA), Parkinson's disease, dementia with Lewy's bodies (DLB), and pure autonomic failure** (PAF) should be considered in the differential diagnosis of OH (Fig. 31.1). Extracellular volume depletion (dehydration), medications, deconditioning, and ageing are frequent exacerbating factors.

D. **Treatment. Treatment of neurogenic OH is directed to improve symptoms and functional capacity and quality of life** (rather than BP "numbers"). The use of diaries (recording symptoms and BP and HR while supine and after standing for <2 minutes, before and 1 hour after meals) facilitates management. Standing times (maximum time a patient is able to stand) can be used in those with severe OH who do not tolerate standing for enough time to allow BP measurements.

1. **Non-pharmacologic treatment is recommended for all patients with neurogenic OH regardless of the cause** (Table 31.5). Countermeasures to raise BP when symptoms of OH are present are keys to successful treatment. Two cups of coffee before meals (breakfast and lunch) may help abate postprandial hypotension.
2. **Pharmacologic treatment. Fludrocortisone acetate is considered the first-line drug in the treatment of OH**. Drugs with vasoconstrictor effects (Table 31.6) should be administered during the patient's active hours to minimize supine hypertension.

SEXUAL DYSFUNCTION

Male and female sexual dysfunction is highly prevalent. Men and women have similar genital and bladder reflexes and lumbosacral innervation. **Genital engorgement is a neurovascular event** controlled by spinal autonomic centers, enhanced by genital stimulation and by supraspinal sexual centers. Up to half of men between 40 and 70 suffer from some degree of erectile dysfunction (ED).

TABLE 31.6 Pharmacologic Treatment of OH

Objective	Mechanism	Drug	Comments
Expand plasma volume	Mineralocorticoid	Fludrocortisone*	>0.1 mg/d
	Antidiuretic	Desmopressin	Vasopressin agonist reduces nocturnal polyuria
Expand red cell volume	↑ red cell mass, blood viscosity	Erythropoietin	Improves orthostatic tolerance in patients with OH and anemia
Enhance vaso-constriction	↑ adrenoceptor sensitivity	Fludrocortisone*	<0.1–0.2 mg/d
		Ibuprofen	400 mg q.i.d. Reduces postprandial OH
	α-adrenoceptor agonist	Midodrine	Monotherapy, or combined with fludrocortisone: 2.5–10 mg b.i.d or t.i.d. As supine hypertension is common, give <4 hr before bedtime
		DOPS	NE precursor, used for DBH deficiency, OH
		Phenylpropanol-amine	5–10 mg q.i.d
	↑ sympathetic ganglionic transmission	Pyridostigmine	Modest increase in BP, with less supine hypertension as compared with other agents
	Vasodilatatory gut peptide antagonist	Octreotide	Reduces postprandial OH. Does not increase supine hypertension

Abbreviations: b.i.d., twice a day; DBH, dopamine- -hydroxylase; DOPS, Droxidopa; q.i.d., four times a day; t.i.d., three times a day; NE, morepimephrime

*Fludrocortisone should be administered with high dietary salt, adequate fluid intake, a potassium-rich diet, and plasma [K^+] should be monitored.

A. Diagnosis. ED is the persistent inability to achieve and maintain an erection sufficient enough to permit satisfactory sexual performance. ED may result as a side effect of medications, or because of neurologic, endothelial, endocrine, metabolic, vascular, and psychogenic causes (depression and anxiety are common causes of sexual dysfunction).

B. Pathophysiology. In men, erection occurs with dilatation of the cavernous helical artery and compression of the cavernous vein against the tunica albuginea. Helical artery dilatation results from activation of cholinergic and nitrergic nerves that release nitric oxide (NO) from the vascular endothelium.

There are three types of erection, each depending on different stimuli:

1. **Psychogenic erection** by audiovisual stimulation (affected by lesions above the sacral cord).
2. **Reflexive erection** by somatosensory stimulation (affected by lesions of the sacral cord and intermediolateral cell columns-as in MSA).
3. **Nocturnal penile tumescence** and morning erection (affected by disturbed rapid eye movement [REM]-sleep).

C. Laboratory testing.

1. Screening blood tests: **morning total testosterone levels** (if low, total and free testosterone, luteinizing and follicle-stimulating hormone, and prolactin levels should be obtained), fasting serum glucose level or HgA1C, and cholesterol and lipid panel.
2. **Further testing for men who do not respond to treatment with phosphodiesterase type 5 (PDE5) inhibitors,** or when specific neurologic causes are considered, or when the cause of ED is not apparent, include glucose tolerance, liver function, prostatic specific

antigen, blood urea nitrogen, creatinine, and thyroid function tests, psychiatric and urologic consultations, and various specialized tests including pharmaco-penile duplex ultrasonography (Doppler and ultrasound of the penis are combined with intracorporeal papaverine) and measurement of penile tumescence or sleep-related erections. When vascular causes are suspected, the appropriate vascular studies are obtained.

Particular attention should be paid to the history of symptoms of leg claudication and psychological symptoms. **As ED is a strong predictor of future cardiovascular disease in younger men, a medical evaluation is recommended.**

D. Treatment of sexual dysfunction.

1. **Management of sexual dysfunction**: Underlying endocrine, metabolic, vascular, and psychogenic causes are treated, and offending medications are adjusted or discontinued. **Exercise, weight loss (goal: BMI <30 kg per m^2), and smoking and alcohol cessation** are recommended for all patients with sexual dysfunction. Pelvic floor muscle strengthening exercises may be helpful. Psychosexual counseling is important in many cases.
2. **Pharmacologic treatment of ED**. **PDE5 inhibitors have revolutionized treatment of ED by their simplicity of use.** They inhibit the destruction of cyclic guanosine monophosphate by PDE5, potentiating smooth muscle relaxation effects of NO on penile blood flow. PDE5 inhibitors do not increase libido and require sexual stimulation to be effective. As NO-mediated smooth muscle relaxation is androgen-dependent, supplementing testosterone in those who are deficient (i.e., morning testosterone <300 ng per dl) may offer benefit.

   Sildenafil (50–100 mg, 1 hour prior to intercourse) and **vardenafil** (10–20 mg, 1 hour prior to intercourse) are shorter-acting agents (duration of effect up to 4 hours), whereas **tadalafil** (10–20 mg, 1–12 hours prior to intercourse) has a longer half-life (duration of effect up to 36 hours). Interaction between PDE5 inhibitors and NO donors (i.e., nitrates) may be precipitate serious hypotension, and the ongoing use of nitrates is an absolute contraindication to the use of PDE5 inhibitors. For patients whose cardiac risk from sexual activity is high, tadalafil should be avoided because of its long half-life.

   Local therapies are indicated in patients in whom PDE5 inhibitors are not effective or contraindicated. Vacuum constriction devices and constriction rings applied to the base of the penis produce unnatural erections but are effective treatment alternatives. Alprostadil, a synthetic analog of prostaglandin E1 (PGE1), increases cAMP, producing penile smooth muscle relaxation and penile erection. The medicated urethral system for erection using alprostadil pellets involves inserting the medication through a small catheter into the urethra. Self-administered injectable medications (papaverine, alprostadil, phentolamine, and PGE1) into the corpus cavernosa to cause an erection are effective. In neurologically normal men, a normal erection in response to the intracavernosal injection of vasoactive agents (i.e., papaverine) indicates that vascular mechanisms involved in erection are intact and may support a diagnosis of psychogenic impotence (although approximately 30% of men with normal erections may lack a response).

URINARY BLADDER DYSFUNCTION

A wide range of neurologic diseases are associated with urinary bladder dysfunction.

A. Physiology.

1. Bladder contraction requires stimulation of parasympathetic cholinergic muscarinic receptors, and relaxation relies on stimulation of β-adrenoceptors. Contraction of the urethra relies on stimulation of α-1A/D adrenoceptors, and relaxation relies on stimulation of nicotinic acetylcholine receptors. Micturition depends on a brainstem and a spinal cord autonomic reflex. It includes periaqueductal gray and the pontine micturition center (PMC), regulated by the hypothalamus and prefrontal cortex. Micturition is initiated by the hypothalamus and prefrontal cortex. The PMC facilitates the sacral bladder preganglionic nucleus and inhibits Onuf's nucleus.
2. Urinary storage relies on a sacral cord autonomic reflex arc. It is tonically facilitated by the pontine storage center, hypothalamus, cerebellum, basal ganglia, and frontal cortex.

B. Clinical presentations.

1. **Urinary urgency/frequency and urgency incontinence. Bladder (detrusor) overactivity** is the most important cause. With lesions above S2–S4, the voiding reflex is intact but overactive because of decreased inhibition from the brain (upper motor neuron bladder). There is inability to sense bladder filling and inhibit bladder emptying, mimicking an exaggerated micturition reflex. Patients with urinary incontinence with urgency usually have upper motor neuron signs at neurologic examination. Causes include dementias, Parkinson's disease, hydrocephalus, bilateral frontal lobe lesion, spinal cord disease, syphilis, and tethered cord. Frequency of micturition is often present in these patients, and bladder capacity is usually reduced. In the elderly, there may be impaired cortical ability to inhibit the voiding reflex with urge incontinence (overactive bladder). The nonneurologic cause of urgency usually is cystitis secondary to infection or inflammation with another cause.
2. **Underactive detrusor (atonic bladder and bladder weakness)** is the major cause of voiding difficulty in autonomic disorders. Typically, it is a "lower motor neuron bladder" as a result of lesions affecting S2–S4 neurons innervating the bladder muscles (although upper neuron lesions can also cause detrusor weakness). There is lack of awareness of bladder filling and inability to initiate voiding producing urinary retention with overflow incontinence. Atonic bladder incontinence occurs in cases of spinal shock, myelitis, conus medullaris and cauda equina lesions, and neuropathy of various types. It also occurs in the course of progressive neurologic diseases, such as MSA, Friedreich's ataxia, tabes, diabetes, alcoholic neuropathy, plexopathy, and after pelvic radiation.
3. **Detrusor hyperactivity with impaired contractile function** (DHIC) reflects lesions in both the storage-facilitating areas (basal ganglia and pontine storage center) and the voiding-facilitating areas (PMC and sacral preganglionic intermediolateral cell column neurons). DHIC is a combination of detrusor overactivity in the filling phase and underactive detrusor in the voiding phase, accompanied by urgency incontinence and difficulty voiding with incomplete emptying (typical findings in MSA).
4. **Detrusor-sphincter dyssynergia** occurs with incomplete relaxation of the urethral sphincter during bladder contraction, and reflects interruption of brainstem–sacral cord micturition reflex pathways. There is often increased residual urine volume with low flow and an intermittent pattern of voiding.
5. **Sphincter weakness** produces urinary stress incontinence or continuous incontinence, and results from lesions involving Onuf's neurons as in MSA.

C. Evaluation of urinary dysfunction. Consultation with a urologist is desirable in the evaluation and management of bladder dysfunction.

1. Bladder neck obstruction must be excluded, especially in the motor paralytic type of bladder dysfunction.
2. Urodynamic investigations include cystometry to provide information about the pressure–volume relation on filling (bladder compliance), bladder capacity, volume at first sensation and at urge to void, voiding pressure, and the presence of uninhibited detrusor contractions (Table 31.7).
3. Sphincter and pelvic floor EMG may detect denervation potentials in selected muscles in lesions of the anterior horn cells in the spinal cord.

D. Treatment.

1. **Incontinence with urgency.**
   a. **Bladder training.** Timed bladder emptying, intermittent catheterization, and biofeedback techniques are used.
   b. **Pharmacotherapy.** Anticholinergic and antimuscarinic agents reduce bladder contraction and alter bladder sensation and capacity, resulting in reduced frequency, incontinence, and increased voided volumes. Duloxetine decreases incontinence episode frequency in women with stress urge incontinence, and imipramine reduces urge and stress incontinence. Botulinum toxin A injections into the detrusor muscle also have been used, especially in cases of neurogenic detrusor overactivity of predominantly spinal cord origin. Table 31.8 provides the dosages of some of the drugs used in the medical management.

TABLE 31.7 Urodynamic Findings in Various Types of Neurogenic Bladder Dysfunction

Spastic Bladder	Atonic Bladder	Sphincter Dyssynergia
Decreased capacity	Increased capacity	Fluctuating voiding pressure
Reduced compliance	Increased compliance	Intermittent flow rate
Uninhibited detrusor contractions	Low voiding pressure and flow rate	

TABLE 31.8 Drugs Used to Manage Bladder Dysfunction

Class of Drug	Drug	Dose
Anticholinergics	Propantheline bromide	15–30 mg q 4–6 h
	Dicyclomine hydrochloride	10–20 mg t.i.d.
	Hyoscyamine sulfate	0.125 mg q 4 h
Antimuscarinic agents	Oxybutynin	5 mg t.i.d. or q.i.d.
	Tolterodine	2–4 mg/d
	Darifenacin	7.5–15 mg/d
	Solifenacin	5–10 mg/d
	Trospium	20–40 mg/d
	Fesoterodine	4–8 mg/d
Tricyclic antidepressants	Imipramine	25 mg t.i.d. or q.i.d.
Serotonin and NE-reuptake inhibitors	Duloxetine	20–40 mg b.i.d.

Dosages of each drug must be individualized to achieve optimum effect with minimum adverse effects. Slow, controlled, or extended release and transdermal preparations are available in some cases and may have less side effects.

2. **Underactive detrusor (atonic bladder with overflow incontinence).** The goal of therapy is to improve bladder tonus and to reduce bladder capacity. The following methods are used:
   a. **Credé's maneuver** or Valsalva's maneuver can empty the bladder.
   b. **Intermittent self-catheterization** is the mainstay of long-term treatment.
   c. Pharmacotherapy usually is not an effective treatment modality. Drugs such as bethanecol in a dosage range of 25 to 100 mg four times a day can be used, but often there are unacceptable side effects.

FECAL INCONTINENCE

A. Clinical features. In upper motor neuron lesions rostral to the sacral cord, there is fecal retention, loss of voluntary control, increased anal sphincter tone, and inability to relax or contract the sphincter on command. Lesions of the sacral cord, conus medullaris, or cauda equina result in a weak and areflexic anal sphincter with a patulous anus. There may also be associated sensory loss. The extent of the sensory deficit and its recovery is important in determining bowel control.

B. Laboratory evaluation. The laboratory studies used in the investigation of fecal incontinence are limited.

1. Proctoscopy and other endoscopic studies, as indicated, demonstrate structural abnormalities.
2. Anorectal manometry assesses internal and external anal sphincter function and measurement of rectal pressure.
3. MRI and CT imaging studies: MRI of the spine (essential in spinal cord lesions) and pelvic CT and/or MRI for some patients with malformations and other structural abnormalities.

4. Endoanal ultrasonography visualizes anal canal musculature and the presence or absence of sphincter defects.
5. Barium enema radiographic examination is helpful in demonstrating obstruction and some structural abnormalities.

C. Neurophysiologic studies. Anal sphincter and puborectalis muscle EMG and pudendal nerve terminal motor latency may provide discriminative evidence of the type of neurologic disorder.

D. Management of fecal incontinence.

1. **Dietary management.** The goal is to increase the volume of the colonic contents and maintain them at near-normal consistency.
   a. Diet high in fiber content.
   b. Docusate sodium to prevent stool hardening.
   c. Psyllium types of dietary fiber to decrease stool viscosity and increase volume.
   d. Some patients may benefit from calcium polycarbophil, an insoluble, synthetic hydrophilic polymer.
2. **Techniques for achieving orderly defecation.**
   a. Valsalva's maneuver and abdominal pressure work for some patients who have preservation of some rectal sensation and feel the urge to defecate.
   b. Glycerine suppositories and digital stimulation of the rectum with a gloved finger work for some patients. These methods are most effective with the patient in the sitting position.
   c. Neural stimulators. Anterior sacral root stimulators (neuromodulation) may be useful in some patients.
   d. Surgical intervention. Formation of a replacement sphincter and pelvic floor reconstruction may be considered in suitable cases.
3. **Biofeedback**. EMG feedback training has been effective for some patients with fecal incontinence.

AUTONOMIC DISORDERS

A. Primary autonomic failure. These are the classic forms of ANS failure for which there is no cure.

1. Pure autonomic failure (PAF), is a degenerative disorder of the ANS of unknown cause, presenting in middle to late life, more often affecting men. The name, PAF, reflects the clinical features with largely isolated **impairment of efferent sympathetic and parasympathetic autonomic neurons** (with relative sparing of the adrenal medulla). There is cell loss in the intermediolateral column of the spinal cord and loss of catecholamine uptake and catecholamine fluorescence in sympathetic postganglionic neurons. As in idiopathic Parkinson's disease and DLB, in PAF there is α-synuclein accumulation in central and peripheral nervous systems, as well as Lewy's bodies. Although the pathology is similar (and PAF may progress clinically to Parkinson's disease with OH and DLB with OH), abnormalities in spinal cord and peripheral nerves are more prominent in PAF, perhaps explaining clinical differences between these disorders.
2. MSA is a progressive, adult-onset neurodegenerative disorder of unknown cause, affecting the autonomic and somatic nervous systems, causing autonomic cardiovascular, urinary, and anorectal dysfunction, parkinsonism, and ataxia in any combination. Onset is typically in the sixth decade of life, and men are affected twice as frequently. In many patients, chronic OH precedes other neurologic involvement, making differentiation of MSA from PAF difficult. Pathology demonstrates glial cytoplasmic inclusions containing α-synuclein and neuronal degeneration at multiple sites within the brain and spinal cord, but no Lewy's bodies. There is no specific diagnostic test, but early urinary and anorectal dysfunction with an abnormal sphincter EMG (because of loss of neurons of the sacral nucleus of Onuf) is typical.

   MSA has been classified as either **MSA-P (parkinsonism)** or **MSA-C (cerebellar)**, depending on the presence of predominant parkinsonism or cerebellar ataxia. As some

clinical features of MSA also occur with other disorders, such as Parkinson's disease and PAF, the clinical diagnosis may be difficult.

a. **Clinical features.** Patients with MSA have OH, erectile and urinary dysfunction, hypohidrosis, early instability, rapid progression, abnormal postures, bulbar and respiratory dysfunction, and emotional incontinence and Parkinsonism and cerebellar features (Table 31.9).

b. **Laboratory evaluation**.

(1) Autonomic testing. See Table 31.3.
Polysomnography may help with the differential diagnosis as REM sleep behavior disorder supports the diagnosis of an α-synucleinopathy (MSA, PD, and DLB). Sleep apnea is more common in MSA than PD and PSP.

(2) EMG may show signs of denervation in limb muscles, suggesting involvement of the anterior horn cells in MSA. Abnormal spontaneous activity or marked motor unit potentials changes in sphincter muscles on an EMG study can distinguish MSA from Parkinson's disease in the first 5 years after the onset of symptoms and signs, and from PAF, as well as from cerebellar ataxias, if other causes for sphincter denervation have been ruled out. EMG does not distinguish MSA from progressive supranuclear palsy. A normal EMG is unlikely in MSA.

(3) MRI. Linear hyperintense putaminal border rim, putaminal atrophy, and putaminal hypointensity relative to the globus pallidus signal are specific to MSA, but sensitivity is low. Cerebellar atrophy may be present in some patients even without clinical cerebellar signs.

(4) Radionuclide gastric emptying study may help evaluate gastroparesis.

TABLE 31.9 Differential Diagnosis of MSA

	Clinical Features	Differential Diagnosis
MSA-P	Non- or poorly levodopa responsive akinetic-rigid syndrome with pyramidal signs, with autonomic dysfunction	• Idiopathic PD • PAF (when MSA has a purely autonomic presentation) • PD presenting with autonomic failure (most MSA with autonomic failure develop other neurologic features within 5 years, but the interval can be longer) • Progressive supranuclear palsy, corticobasal degeneration, primary lateral sclerosis, amyotrophic lateral sclerosis (slowing, spasticity and pyramidal signs may be confused with a levodopa-unresponsive akinetic-rigid syndrome with pyramidal signs similar to MSA. The characteristic eye movement findings of these are absent in MSA) • Cerebrovascular disease
MSA-C	ILOCA syndrome with autonomic dysfunction	• ILOCA syndrome (25% have MSA) • Friedreich's ataxia (atypical, late onset form) • SCA 2, 3 and 6 (cerebellar features and parkinsonism, with family history in SCA 2 and 3, sporadic in SCA 6) • Primary progressive multiple sclerosis, fragile X tremor ataxia syndrome, sporadic adult onset ataxia, and sporadic cerebellar-olivary atrophy

Abbreviation: ILOCA, idopathic late onset cerebellar ataxia; SCA, spinocereballar ataxia.

c. **Management.** Only symptomatic treatment is available. One-third of patients have temporary response to levodopa; some may respond to amantadine. Side effects, especially accentuation of hypotension, must be kept in mind.
d. **Dopamine β-hydroxylase deficiency** is a rare inherited disorder characterized by an inability to metabolize dopamine to NE, with sympathetic and adrenomedullary failure, but normal parasympathetic and sympathetic cholinergic function. There is minimal or absent plasma NE and epinephrine with marked elevation of plasma dopamine. Symptomatic treatment involves administration of L-DOPS, a synthetic NE precursor.

AUTONOMIC NEUROPATHIES

A. **Diabetic autonomic neuropathy** (DAN) is a common complication of diabetes. As a length-dependent neuropathy, DAN affects the vagus nerve early on with abnormal cardiovascular autonomic function, manifested as reduced HR variation, the earliest indicator of cardiac autonomic neuropathy (CAN). Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes. The 5-year mortality rate is five times higher for those with CAN than for individuals without cardiovascular autonomic involvement. Impaired glucose regulation (IGT, non-diabetic hyperglycemia, prediabetes) with small fiber neuropathy is accompanied by mild autonomic neuropathy (sudomotor fibers tend to be affected earlier with IGT).
B. **Amyloid autonomic neuropathy:** common in both primary and familial amyloidosis, but uncommon in secondary amyloidosis.
C. **Acute and subacute autonomic neuropathies:** acute inflammatory demyelinating polyradiculoneuropathy, subacute autonomic neuropathy (pandysautonomia, sympathetic and cholinergic dysautonomias).
D. **Immune-mediated and paraneoplastic neuropathies:** Paraneoplastic autonomic neuropathy, autoimmune autonomic ganglionopathy, Lambert Eaton myasthenic syndrome. May be initial presentation of cancer.
E. **Hereditary autonomic neuropathies:** Familial amyloidotic, hereditary sensory and autonomic (Familial dysautonomia), hereditary motor and sensory, Friedreich's ataxia, porphyria, Fabry's disease, Navajo sensory-autonomic neuropathy with arthropathy.
F. **Autonomic neuropathy because of infectious diseases:** Chagas disease, HIV, leprosy, botulism.
G. **Autonomic neuropathies because of toxins:** alcohol, drugs (amiodarone, cis-platinum, cyclosporine A, vincristine, perhexiline, Taxol), heavy metals, toxins (acrylamide, hexacarbons, Taxol).
H. **Autonomic neuropathies because of deficiency states:** vitamin B12.

AUTONOMIC CRISIS

A. **Autonomic crises.** Acute autonomic dysfunction occurs in many conditions and a hypersympathetic state is most often encountered. Examples of such neurologic conditions are as follows.
1. Cerebral lesions: ischemic stroke, intracerebral hemorrhage (ICH), subarachnoid hemorrhage, intracranial mass lesion, Cushing response.
2. Spinal cord lesions.
3. Peripheral nerve disease: Landy–Guillain–Barré's syndrome.
4. Systemic diseases: tetanus, episode of acute intermittent porphyria.
5. Drug-related conditions: neuroleptic malignant syndrome, sympathomimetic drug overdose, tricyclic antidepressant overdose.

B. **Autonomic dysreflexia** is a sympathetic storm that occurs in cases of spinal cord transection. The spinal cord lesion usually is above the midthoracic level. The episodes are paroxysmal and start several months after the acute spinal cord injury as recovery occurs. The episodes are characterized by sudden onset of severe hypertension,

headache, sweating and flushing, piloerection, and sometimes chills. A precipitating cause can most often be identified and is a noxious stimulus. Urinary bladder distention and fecal impaction are common causes. Elimination of the precipitating cause often results in resolution of the episode and prevention is the best therapy. Hypertension is treated with antihypertensive agents with rapid onset and short duration.

Recommended Readings

Appell RA. Pharmacotherapy for overactive bladder. *Drugs.* 2006;66:1361–1370.

Benarroch E. The arterial baroreflex. Functional organization and involvement in neurological disease. *Neurology.* 2008;71:1733–1738.

Benarroch E. Neural control of the bladder. Recent advances and neurologic implications. *Neurology.* 2010;75; 1839–1846.

Bradley WG, Daroff RB, Fenichel GM, et al., eds. *Neurology in Clinical Practice.* 4th ed. Boston, MA: Butterworth-Heineman; 2004.

Cirino G, Fusco F, Imbimbo C, Mirone V. Pharmacology of erectile dysfunction in man. *Pharmacol Ther.* 2006;111:400–423.

Ehrenpreis ED, Chang D, Eichenwald E. Pharmacotherapy for fecal incontinence: a review. *Dis Colon Rectum.* 2006;50:641–649.

Fowler CJ. Electrophysiologic evaluation of sexual dysfunction. In: Low PA, ed. *Clinical Autonomic Disorders, Evaluation and Management.* 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1997.

Fowler CJ. Integrated control of lower urinary tract—clinical perspective. *Br J Pharmacol.* 2006;147:S14–S24.

Freeman R. Autonomic peripheral neuropathy. *Neurol Clin.* 2007; 25:277–301.

Garg BP. Disorders of micturition and defecation. In: Swaiman KF, Ashwal S, Ferriero DM, eds. *Pediatric Neurology: Principles and Practice.* 4th ed. St. Louis, MO: Mosby; 2006.

Husmann DA. Use of sympathetic alpha antagonists in the management of pediatric urologic disorders. *Curr Opin Urol.* 2006;16:277–282.

Ku JH. The management of neurogenic bladder and quality of life in spinal cord injury. *BJU Int.* 2006;98:739–745.

Lagi A, Spini S. Clinostatic hypertension and orthostatic hypotension. *Clin Cardiol.* 2010;33:E10–E15.

Maslekar S, Gardiner A, Maklin C, Duthie GS. Investigation and treatment of fecal incontinence. *Postgrad Med J.* 2006;82:363–371.

Oribe, E: Testing autonomic function. In: Appenzeller O, ed. *The Autonomic Nervous System. Part 1—Normal Functions.* Amsterdam and New York, Elsevier Science; 1999. Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology.*

Podnar S. Neurophysiology of the neurogenic lower urinary tract disorders. *Clin Neurophysiol.* 2007;118:1423–1437.

Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. *Lancet.* 2007;369: 512–525.

Robertson D. The pathology and diagnosis of orthostatic hypotension. *Clin Auton Res.* 2008;18(suppl 1):2–7.

Wein AJ, Kavoussi LR, Novick AC, et al., eds. *Campbell-Walsh urology.* 9th ed. Philadelphia, PA: WB Saunders; 2007.

Woderich R, Fowler CJ. Management of lower urinary tract symptoms in men with progressive neurological disease. *Curr Opin Urol.* 2006;16:30–36.

CHAPTER

32 Neuroimaging of Common Neurologic Conditions

Jordan Rosenblum

Most common neurologic conditions are imaged using CT, MRI, or both. In the emergent setting, CT is still the most commonly utilized modality. Patients with trauma or a suggestion of acute intracranial hemorrhage are routinely imaged with CT scans, whereas those with findings suggestive of ischemic stroke may be triaged to either CT or MRI. Frequently, the decision rests on the availability of the modality and the time needed to obtain the study. Advances in neuroimaging allow greater specificity in identifying metabolic and physiologic differences between normal tissue and pathology. Some of the most exciting advances include the use of diffusion-weighted imaging (DWI) with MRI that can demonstrate physiologic change within minutes of ischemic change, MR spectroscopy that can identify abnormal metabolites and help in differentiating pathology such as recurrent tumor versus radiation necrosis, and functional MRI (fMRI) that can be used to localize specific functional areas in the brain. The choice of most appropriate imaging modality is presented according to clinical presentation. The information available with medical imaging carry with it specific risks that must be balanced against diagnostic gain. Ionizing radiation from CT may result in significant radiation dose, especially when multisequence scans are performed. Although the actual risk of cancer induction is still an open debate, it is clear that scans should only be ordered that are absolutely necessary and that will affect patient management. Other risks to consider from imaging have been described from contrast use in both CT and MRI. Iodinated contrast can lead to a contrast-induced nephropathy in patients with preexisting renal insufficiency. Recently, gadolinium contrast has been linked to nephrogenic systemic fibrosis (NSF), a rare scleroderma-like systemic disease in patients with renal insufficiency. Current recommendations are to either forgo gadolinium contrast in patients in moderate renal insufficiency, or if medically indicated, reduce the dose and use one of the agents believed to be associated with less risk of NSF. Patients with severe renal failure should in most cases not receive gadolinium contrast.

I. TRAUMA

CT is the primary imaging modality in trauma because of ready availability, speed, ability to detect bony abnormalities, and superior accuracy in detecting acute intracranial blood. High-resolution, fast CT scanners are routinely installed either within emergency departments or in close proximity. CT is performed routinely in trauma patients, often including those without focal neurologic signs to screen for occult injury. Widely accepted standards for patient selection in this setting are still controversial.

MRI in the setting of acute trauma is still a secondary modality. The most important indication is in evaluating for diffuse axonal injury in which diffuse brain injury may be seen in the presence of a normal head CT. MRI may also demonstrate small extra-axial hemorrhages not seen by CT, particularly in the subtemporal and subfrontal regions.

A. Closed head injury. CT imaging parameters in trauma should include a narrow window (for acute blood), an intermediate window (for subacute blood), and a wide (bone) window. Acute blood may be present in the form of intracerebral (contusion), epidural, or subdural hematomas and subarachnoid hemorrhage (SAH). Fractures are well-evaluated on bone windows and from coronal and sagittal reconstruction images. Patients with acute trauma and favorable initial coma scores usually fare well and do not require extensive follow-up imaging. In patients with moderate or severe trauma, or low initial Glasgow Coma Score, sequential CTs allow evaluating the course of the initial trauma and the effects of therapy, including extension of initial hemorrhage, rehemorrhage, cerebral edema, herniation,

response to external ventricular drainage, and intracranial pressure monitors. Diffuse cerebral edema, more common in younger patients, causes effacement of CSF spaces and may result in herniation (tonsillar, transtentorial, and subfalcine). In patients who come to medical attention several days or weeks after head trauma, with worsening headaches or seizures, MRI may be preferred because subacute hematomas may be isodense on CT, and therefore difficult to see. MRI is superior in evaluating for the presence of blood products in the brain parenchyma (Fig. 32.1A and B).

B. Penetrating head injury. CT is the modality of choice in patients with penetrating head injuries. Metallic objects (shrapnel) and glass appear hyperdense on CT, whereas wood objects appear hypodense (air-containing). CT permits an excellent evaluation of the extent of bone damage, and that of the underlying parenchyma, including hematomas, edema, infarction, and herniation.

C. Cervical spine injury. Plain X-rays remain the first-line imaging method in patients with cervical spine trauma and should include at least anteroposterior, lateral, and open-mouth (odontoid) views. Cervical spine CT offers submillimeter resolution allowing the detection of subtle fractures not seen on plain films. MRI is used to evaluate for spinal cord injury, which appears bright on T2 pulse sequences and dark on gradient echo sequences because of the magnetic susceptibility effect of acute blood.

D. Vascular injury. Blunt injury to the neck may result in traumatic arterial dissections, pseudo-aneurysms, or occlusions. In stable patients, magnetic resonance angiography (MRA) or CT angiography (CTA) are excellent imaging methods. Unstable patients may go directly to angiography, particularly if endovascular management is contemplated. Penetrating injuries may result in similar lesions, in addition to significant bleeding from both arterial and venous (jugular vein) injuries. CTA is the imaging method of choice in these patients because current fast scanners allow the evaluation of large anatomical areas with high-resolution and limited-contrast administration. Unstable patients may also require emergency angiography and possibly lifesaving endovascular occlusion of a bleeding artery.

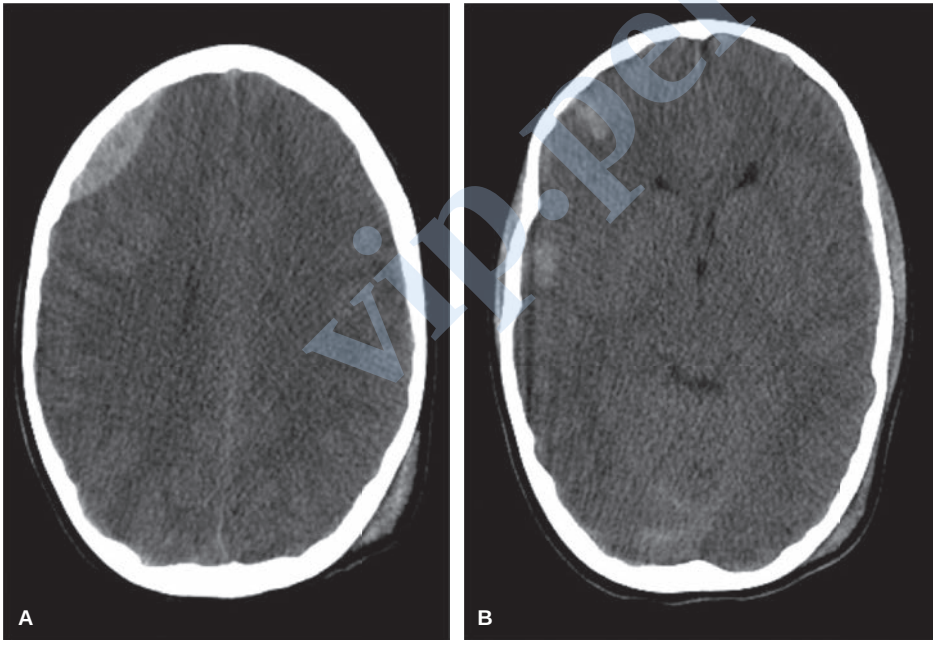

FIGURE 32.1 CT of a 10-year-old boy who fell from a tree. Noncontrast head CT demonstrates a right frontal epidural hematoma **(A)** and parenchymal contusions **(B).**

II. HEADACHES

Headache is one of the most common indications for neurologic consultation, with 50% of adults being seen for a severe headache at least once in their life. Fortunately, the vast majority have a benign origin. Pain sensitive structures in the cranial area include the scalp, the scalp blood vessels, head and neck muscles, dural sinuses, the dura and large cerebral arteries at the skull base, meningeal arteries, and pain sensitive fibers of the fifth, ninth, and tenth cranial nerves. Serious conditions that cause headaches include hemorrhage (subarachnoid, subdural, and intracerebral), infections (meningitis and brain abscess), tumors (primary or metastatic), hydrocephalus, and hypertensive crises. Patients at higher risk for significant pathology include those with (1) severe headache of sudden onset; (2) mental status changes, fever, focal neurologic deficits, or seizures; and (3) onset after the age of 50.

A. Acute headaches. Acute headache associated with nausea, vomiting, nuchal rigidity, and transient alteration in mental status is suggestive of SAH and should prompt immediate evaluation. CT is currently the preferred neuroimaging method for SAH, with reported accuracy rates in the 98% to 99% range.

1. **SAH and aneurysms.** Nontraumatic SAH is caused by a ruptured intracranial aneurysm in 80% to 85% of adult patients (Fig. 32.2A and B). About 10% of patients with SAH, usually in the younger age group, have a nonaneurymal perimesencephalic hemorrhage, a benign and self-limiting venous hemorrhage. Catheter angiography remains the gold standard to evaluate SAH, followed by endovascular or surgical aneurysm obliteration if an aneurysm is identified. CTA is increasingly used as a reliable replacement for cerebral angiography, including for the surgical planning of ruptured and unruptured aneurysms. Uncommon causes of SAH include cerebral and dural arteriovenous malformations (AVMs), arterial dissections, cerebral tumors, vasculitides, and moyamoya disease.
2. **Intracerebral hemorrhage and other causes of acute headache.** Intracerebral hemorrhage is most commonly caused by arterial hypertension and may be putaminal, thalamic, lobar, cerebellar, or pontine. Cerebral amyloid angiopathy may cause lobar hemorrhage in the nonhypertensive elderly. CT is the primary method of evaluation. In younger, nonhypertensive patients, a cerebral or dural AVM may be the cause of hemorrhage, requiring further workup with MRI and cerebral angiography, which may

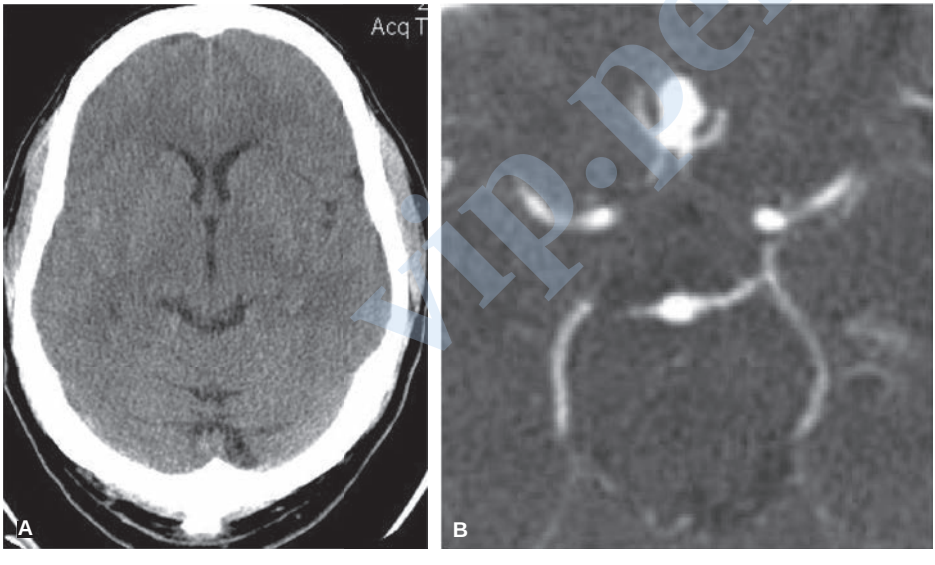

FIGURE 32.2 CT of a 38-year-old woman with acute onset severe headache. Noncontrast head CT demonstrates subtle subarachnoid blood in right sylvian fissure **(A).** CTA demonstrates an anterior communicating artery aneurysm **(B).**

need to be repeated or delayed if there is a large and compressive hematoma. Contrast-enhanced MRI and possibly MR spectroscopy may be useful if a tumor is suspected.

Severe unilateral headache with cervicalgia and/or a Horner syndrome may be caused by an acute carotid or vertebral arterial dissection. MRI/MRA, especially with precontrast fat-saturated axial T1 imaging, is diagnostic, showing the true lumen as a flow void and the mural thrombus as a bright crescent, so that there is generally no need for conventional angiography unless intracranial extension is suspected or endovascular treatment is contemplated. Migraines can cause severe acute headaches, usually periorbital, hemifacial, and frontal. The diagnosis is clinical, and CT may be sufficient to rule out hemorrhage in typical cases. Sinusitis is also diagnosed clinically; coronal CT shows soft tissue material obstructing sinus drainage pathways and filling the sinuses, and air–fluid levels in acute sinusitis. Glaucoma, retrobulbar optic neuritis, hydrocephalus, and infection may also cause acute headaches, evaluated with CT in clinically uncertain cases.

B. Subacute headaches. Subacute headaches, particularly in the elderly, may be caused by a subdural hematoma. CT is usually adequate for both the initial evaluation and the follow-up, showing subdural space crescentic collections. Acute blood is hyperdense, whereas chronic collections are hypodense. CT is also the modality of choice to diagnose hydrocephalus (the temporal horns and the third ventricle are early reliable indicators of hydrocephalus). Cerebral tumors and infections may be evaluated with postcontrast CT (although contrast-enhanced MRI is superior). Spontaneous intracranial hypotension, possibly associated with a chronic CSF leak, is a potential cause for headaches causing recurrent ER visits; postcontrast MRI (particularly in the coronal plane) may be diagnostic, showing thickened and densely enhancing meninges as well as "sagging of the midbrain" and decreased volume in the suprasellar and basilar cisterns.

C. Chronic headaches. Unruptured AVMs, temporal arteritis, vasculitides, colloid cysts of the third ventricle, and cervical spondylosis are all potential causes of chronic headaches, in addition to migraine, cluster headaches, and chronic sinusitis. MRI has the highest yield in screening patients with a suspected structural intracranial anomaly.

III. CEREBRAL ISCHEMIA

Cerebral ischemia may be the result of acute arterial occlusion, hypoxic or anoxic injury, or may result from venous occlusion with increased venous pressure. Arterial occlusion may be an acute event, a chronically progressive process or an acute process superimposed on chronic.

A. Acute stroke. It is a true emergency (time is brain). There is a 4.5-hour window after the ischemic stroke onset for the delivery of intravenous tissue plasminogen activator. Past that, and up to 6 hours in the carotid circulation (possibly longer in the vertebrobasilar circulation), intra-arterial thrombolysis may be an option. One proposed algorithm for the emergency evaluation of acute stroke is to obtain a plain CT, followed (if no hemorrhage) by a contrast CTA and CT perfusion study to evaluate the perfusion deficit. In some centers, MRI, MRA, and MR perfusion are utilized in acute stroke patients. DWI is positive for acute stokes as early as 30 minutes and up to 10 days after the onset and is therefore particularly well-suited to differentiate acute and subacute from chronic events (Fig. 32.3A and B).

B. Dural sinus and cortical vein thrombosis. The venous intracranial circulation should always be evaluated, particularly if the patient's neurologic deficit is accompanied by headache or does not fit a recognizable vascular distribution. Recent thrombus within a dural sinus may be difficult to identify on plain CT (although possibly seen as a spontaneously hyperdense filling structure) or on plain MRI (hyperacute blood may appear gray on both T1 and T2 sequences). Therefore, postcontrast imaging (CT and MRI) has higher accuracy, showing clots as filling defects within a dural sinus or cortical vein. An MR venography (MRV) provides 3-D visualization of the venous system, which may be selectively imaged owing to its lower velocity profile compared with arterial structures (Fig. 32.4A and B).

C. Intermittent and chronic deficits. Transient ischemic attacks (TIAs) and chronic ischemic deficits are best evaluated with MRI/MRA. DWI MRI is most often normal in TIAs and ischemic lesions 10 days or older. MRI is superior to CT in evaluating stroke mimics including demyelinating disease and tumor. MRA is effective in screening the intracranial and cervical arterial vasculature although the resolution of CTA (0.625 mm with current 64-detector scanners) provides excellent definition, nearing

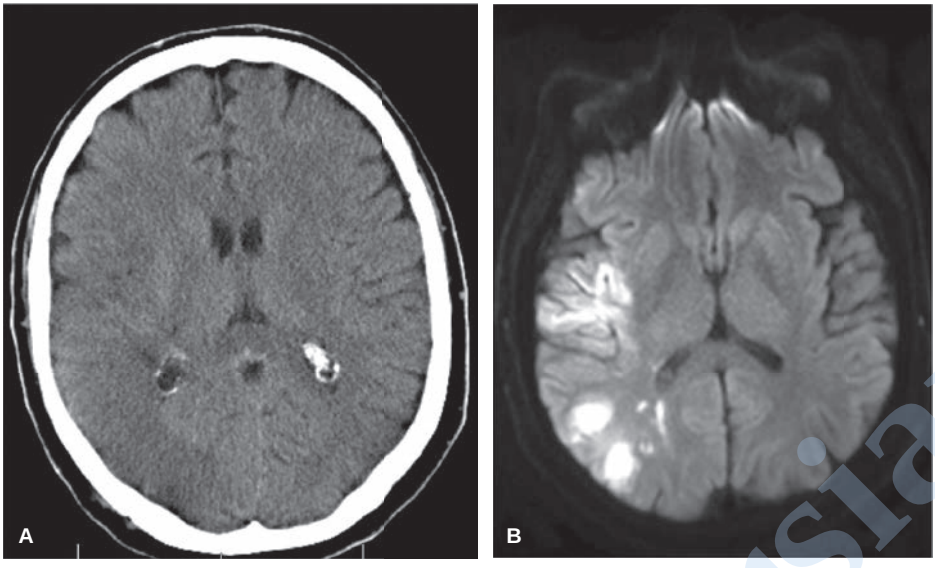

FIGURE 32.3 Noncontrast head CT demonstrates an area of hypodensity in the right temporal region **(A).** Diffusion weighted MRI scan **(B)** demonstrates larger area of restricted diffusion, consistent with acute ischemic change.

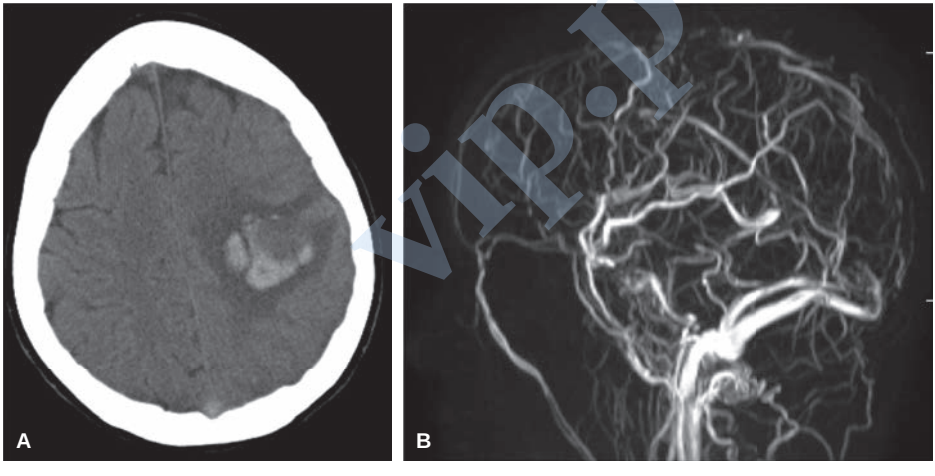

FIGURE 32.4 Severe headache and mental status changes. Noncontrast head CT demonstrates parenchymal hemorrhage in the left hemisphere with high density noted in the superior sagittal sinus **(A).** MRV demonstrates absent signal in the superior sagittal sinus consistent with sinus thrombosis **(B).**

that of conventional angiography in certain locations. Severe arterial stenoses are a known pitfall of MRA, which exaggerates the degree of the lesion owing to signal loss. Therefore, conventional angiography remains useful in equivocal cases whenever corrective therapy is contemplated.

IV. ALTERED LEVEL OF CONSCIOUSNESS

Evaluation of a patient with an altered level of consciousness (LOC) a common indication for neurologic consultation requiring immediate neuroimaging. Causes of altered LOC may include intracranial hemorrhage (including traumatic), stroke, metabolic disorders, toxic substance ingestion (suicide attempts or accidental), and cerebral tumors (primary or metastatic).

The immediate concern in these patients is to rule out a major indication for emergent intervention, including intracranial hemorrhage, acute infarctions, impending tonsillar or transtentorial herniation, or other life-threatening conditions. CT scanning is the preferred modality in these patients because of ready access and accuracy in identifying intracranial hemorrhage (intracerebral, SAH, SDH, and epidural). It is also possible to assess the risk for herniation if a lumbar is indicated to rule out SAH or infection. In patients without CT evidence of acute abnormal findings, MRI should be obtained as soon as to detect CT occult process including dural sinus thrombosis, acute basilar artery thrombosis, and posterior reversible encephalopathy syndrome, which show characteristic T2 and FLAIR cortical and subcortical lesions.

V. DEMENTIA

Cognitive decline may be related to a number of clinical conditions including (1) depression, (2) structural lesions (cerebral tumor, subdural hematoma, and hydrocephalus), (3) chronic cerebral ischemia, or (4) primary neurodegenerative conditions, the most common of which is dementia of the Alzheimer's type (DAT). A thorough clinical evaluation plays a major role in these patients who are often in the older age group. Neuroimaging detects correctable causes of dementia, found in about 5% of patients with progressive cognitive decline. CT is adequate to identify severe hydrocephalus and chronic subdural hematomas. However, MRI is superior to CT in the vast majority of patients, although unfortunately effective therapy is available in only a few conditions. Assessment of generalized cerebral and focal hippocampal atrophy in DAT is more easily done with MRI, including computerized volumetric measurements of the hippocampus. PET and SPECT may allow detection of DAT earlier by showing decreased hippocampal glucose metabolism. Also MRS may show increased myo-inositol and decreased *N*-acetyl-aspartate peaks in the gray matter. Vascular dementia is also well-evaluated by MRI, particularly FLAIR imaging, which demonstrates lacunar infarcts and white matter abnormalities. Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) may have a typical distribution (periventricular, anterior temporal, and subinsular) that may suggest the diagnosis (Fig. 32.5A and B). In Pick's disease and other frontotemporal dementias, predominance of frontal lobe atrophy is well-evaluated on multiplanar MRI. In suspected normal pressure hydrocephalus, transependymal CSF flow may be present, seen as periventricular bright T2 signal. The pattern and velocity of CSF flow may be evaluated at the foramen magnum using phase contrast flow techniques.

VI. SEIZURES

A. New onset adult seizures. Although patients presenting with seizures are often scanned initially with CT to rule out hemorrhage or tumor, MRI is the preferred initial imaging method to investigate new onset adult seizures, owing to its superior contrast

resolution and multiplanar capability. Magneto-encephalography (MEG) is a new technique that measures magnetic fields caused by neuronal activity, with a spatial resolution of a few millimeters and a temporal resolution of milliseconds. Magnetic source imaging uses MEG in combination with MRI in the same machine and has currently the highest

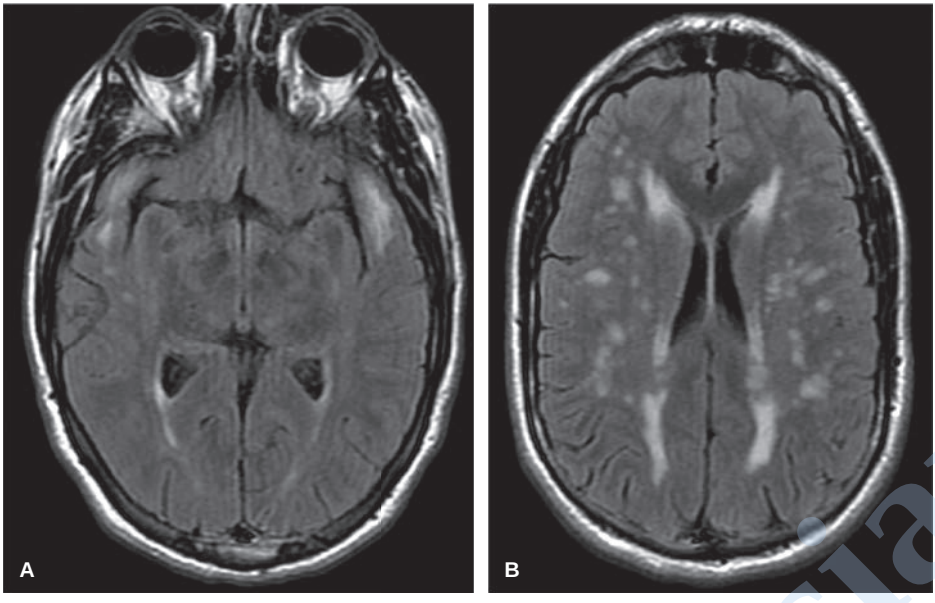

FIGURE 32.5 Forty-one-year-old man with migraines with aura, TIAs, and cognitive decline diagnosed with CADASIL. Axial FLAIR images at the level of the lateral ventricles **(A)** and through the temporal lobes **(B)** demonstrates scattered areas of signal abnormality. The symmetric anterior temporal lobe abnormalities are typical in this disease.

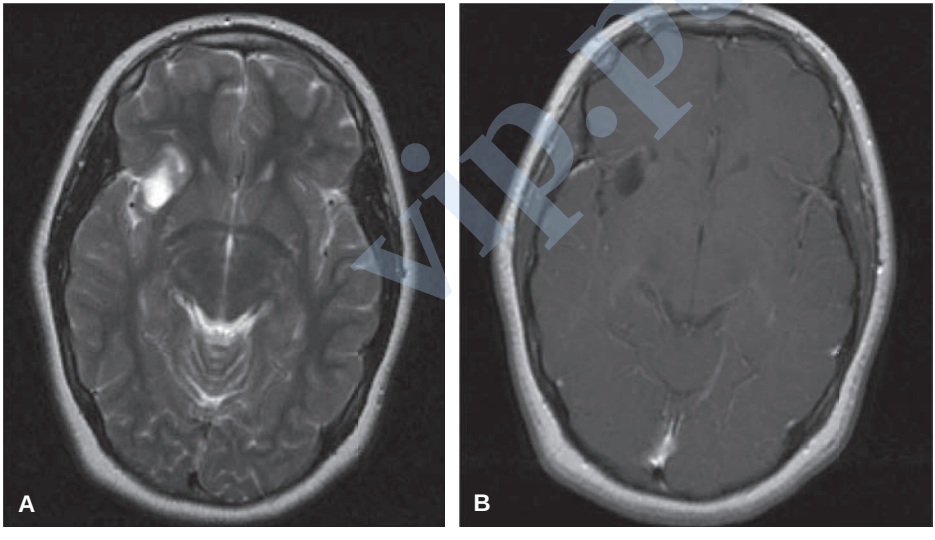

FIGURE 32.6 T2 axial image demonstrates abnormal signal in the inferior right frontal lobe **(A).** Postcontrast T1 axial image **(B)** demonstrates a minimally enhancing cystic ganglioglioma in this 19 year old with a history of seizures.

yield detecting epileptogenic foci. New onset adult seizures may be caused by tumors (primary or metastatic), AVMs, inflammatory conditions, vasculitides, ischemic lesions, and gliosis from prior injury (Fig. 32.6A and B).

B. Known seizure disorder. In patients with temporal lobe epilepsy, coronal MRI (FLAIR and T2) has a high overall detection rate (up to 80%) for mesio-temporal sclerosis, showing an atrophic hippocampus with high T2 signal and indirect signs including dilated choroidal fissure and forniceal atrophy. Presurgical evaluation includes the evaluation of hemispheric language dominance, usually obtained by Wada's testing (selective internal carotid artery injection of sodium amobarbital). The fMRI has been used to detect language dominance, although its accuracy is as of yet unproven compared with Wada's test.

C. Pediatric seizures. Infants with germinal matrix and traumatic hemorrhages, intracranial neonatal infections, and perinatal ischemia may be evaluated and followed with CT. In stable, nonfebrile infants, most neonatal seizures are related to congenital disorders (migrational anomalies and structural defects), which are best evaluated with MRI, although traumatic lesions are detectable on CT. In childhood-onset seizures, clinical and EEG evaluations are usually adequate and imaging may not be necessary for certain forms of seizure activity, including febrile, absence (petit mal) seizures, infantile spasms (Lennox–Gastaut's syndrome), and benign focal epilepsy, unless the child has abnormal physical findings or delayed development. Certain forms of childhood epilepsy, like juvenile myoclonic epilepsy, are associated with a higher frequency of structural anomalies requiring MRI evaluation.

VII. HEARING LOSS AND TINNITUS

A. Hearing loss. Clinical and audiometric data should guide neuroimaging. The deficit may be (1) sensorineural (SNHL), conductive (CHL) or mixed; (2) unilateral or bilateral; and (3) congenital or acquired.

1. **Sensorineural hearing loss.** Unilateral or asymmetrical SNHL in adults is best evaluated with MRI. The most common cause is a vestibular schwannoma. Even small lesions of the internal auditory canal and cerebellopontine angle are diagnosed with thin T1, T2, and postcontrast axial and coronal MRI, and the addition of a high-resolution volume (**F**ast **I**maging **E**mploying **S**teady s**T**ate **A**cquisition). MRI should also evaluate the remainder of the acoustic pathway for possible ischemic or demyelinating lesions, particularly the medullary cochlear nuclear complex (which lesions mimic those caused by vestibular schwannomas), thalamus, and temporal lobe (see Fig. 56.2).

   SNHL in children, unilateral or bilateral, is usually related to congenital inner ear diseases, requiring high-resolution noncontrast CT as the initial evaluation to assess the cochlea, vestibule, semicircular canals, vestibular aqueduct, and endolymphatic duct and sac. Enlarged vestibular aqueduct syndrome is a common cause of SNHL.

2. **Conductive hearing loss.** CHL is caused by disruption of the mechanical components of the auditory apparatus. CHL is therefore best evaluated by noncontrast high resolution CT. It is most commonly caused by temporal bone inflammatory disease, particularly otomastoiditis and otitis media. Otosclerosis (also called otospongiosis) causes both CHL and SNHL (bilateral in 80%) and tinnitus. It is because of the replacement of endochondral bone by spongious bone at the oval window (fenestral) or the cochlea (retrofenestral). Other causes for CHL include middle ear cholesteatomas, tumors (glomus tympanicum), and traumatic ossicular dislocations, all well-evaluated with CT.

B. Tinnitus. It (ringing in the ear) may be very disturbing to patients. It may be pulsatile or nonpulsatile. Objective tinnitus, heard by both the patient and the examiner, commonly leads to findings. Subjective tinnitus, only heard by the patient, has a low diagnostic yield.

1. **Pulsatile tinnitus.** Pulsatile (pulse synchronous) tinnitus is best evaluated by MRI/MRA, whether or not direct otoscopic examination shows a retrotympanic mass. A vascular-appearing tympanic membrane may be associated with arterial (aberrant carotid artery, carotid stenosis or dissection, and petrous carotid artery aneurysms),

venous (dehiscent or high-riding jugular bulb), inflammatory (cholesterol granuloma, middle ear mastoiditis) causes or tumors (glomus tympanicum or jugulo tympanicum and meningioma). Tinnitus with a normal otoscopic examination should raise suspicion for a dural arteriovenous fistula (of the sigmoid sinus or the tentorium); MRI may show suspicious flow voids, MRA source images may demonstrate transosseous arterial structures, and postcontrast MRI and MRV may demonstrate an occluded dural sinus. Confirmation (and therapy) is provided via catheter angiography. Other conditions include venous sinus stenosis, idiopathic intracranial hypertension (pseudotumor cerebri), chronic anemia, and thyrotoxicosis.

2. **Nonpulsatile tinnitus.** It is most commonly caused by Ménière's disease, which also manifests as episodes of vertigo and SNHL. Increased volumes of endolymph causing enlarged endolymphatic spaces have been incriminated. The diagnosis is clinical, but when indicated, neuroimaging should be done with CT. Other causes include otosclerosis and middle ear inflammatory disease, also best studied with CT.

VIII. VERTIGO AND ATAXIA

Vertigo and ataxia may indicate posterior fossa lesions where MRI is the modality of choice because of superior contrast resolution and beam hardening artifact with CT.

Causes of vertigo that may be diagnosed with imaging include vestibular schwannomas, viral labyrinthitis, or perilymphatic fistulae. Central vertigo may be caused by posterior fossa lesions including demyelinating disease, tumors, strokes, Arnold–Chiari malformation, and trauma. The preferred neuroimaging method to investigate vertigo is MRI. Even small

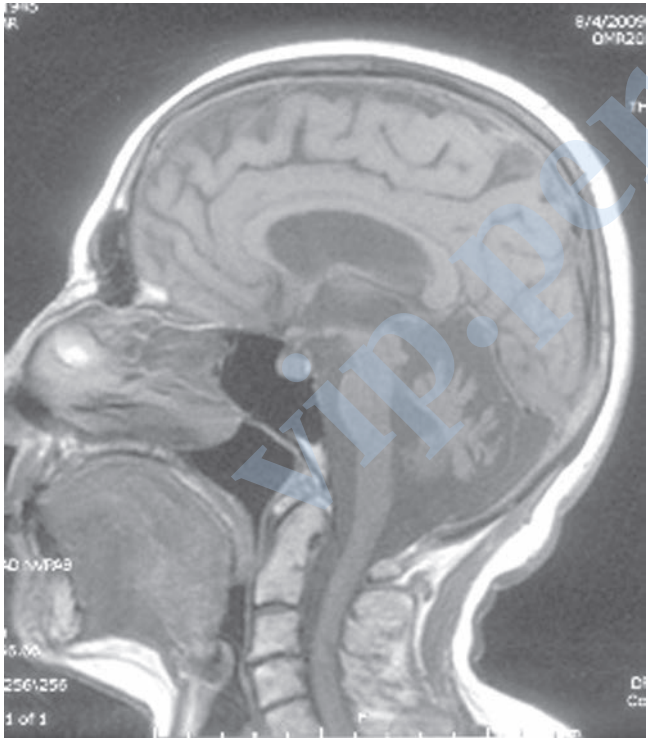

FIGURE 32.7 Sagittal T1 image demonstrates prominent volume loss of the cerebellum, pons, and brainstem, in this patient with multiple system atrophy of the cerebellar type (olivopontocerebellar atrophy).

vestibular schwannomas may be diagnosed with a good quality MRI, appearing as small enhancing masses. Rarely, viral labyrinthitis will show as bright T1 signal within the vestibular apparatus indicative of hemorrhagic products. Small multiple sclerosis plaques and ischemic lesions appear as bright lesions on T2 and FLAIR imaging.

Ataxia usually reflects cerebellar dysfunction, although it may also be sensory or vestibular in origin. Again, MRI is the preferred imaging modality to study patients with ataxia because of its superior contrast resolution in demyelinating diseases, ischemia, and tumors. Other causes of ataxia include chronic ethanol and phenytoin intoxication, a number of degenerative conditions, paraneoplastic syndromes, all accompanied with cerebellar atrophy, well-demonstrated on sagittal and coronal MRI (Fig. 32.7).

IX. DISTURBANCES OF VISION

The optic pathways and the globe are both well-evaluated with MRI, which is the preferred neuroimaging study in patients with visual disturbance.

A. Visual loss (including amaurosis fugax). Gradual monocular vision loss is usually related to ocular pathology like cataract. Sudden unilateral vision loss most commonly results from diabetic retinopathy, followed by ocular ischemic syndrome, which may be caused by retinal vein occlusion, retinal artery occlusion, anterior ischemic optic neuropathy, an ischemic syndrome of the anterior ciliary vasculature, and rarely to demyelinating disease of the optic nerve, well-evaluated with pre- and postcontrast MRI. Amaurosis fugax designates vision loss caused by reduced blood flow to the eye, heralding a stroke and prompting therapy. The most common cause of amaurosis fugax is stenotic carotid disease, which is well-evaluated by MRA. CTA is an excellent alternative to evaluate carotid disease, although heavily calcified plaques remain a limitation.

Visual field deficits related to lesions affecting the optic chiasm, tracts, and radiations should be studied with contrast-enhanced MRI. Lesions affecting the chiasm, like pituitary adenomas, and suprasellar lesions are particularly well-suited for coronal and sagittal MRI. Most demyelinating and inflammatory conditions and tumors involving the postchiasmatic optic pathways appear bright on T2 and FLAIR imaging and enhance after contrast administration. Cerebral AVMs of the temporal and occipital lobes appear as dark, tortuous flow voids on T1 and T2 imaging.

B. Impairment of ocular motility. Ocular motility dysfunction most commonly results from diabetic cranial neuropathy and traumatic lesions of the orbit or the superior orbital fissure. Traumatic lesions involving bony structures are best evaluated with thin-cut CT with coronal reconstructions. Nontraumatic pathology may result from a variety of lesions affecting the oculomotor, trochlear, and abducens nerves anywhere between their brainstem nuclei and the orbit including brainstem strokes, demyelinating and inflammatory lesions, tumors, petrous apex lesions, cavernous sinus and orbital apex tumors, aneurysms, and inflammatory lesions. MR is the modality of choice in evaluating all of these possibilities. A sudden third cranial nerve palsy suggestive of an internal carotid artery—posterior communicating artery junction aneurysm may be initially evaluated with either MRI/MRA or CT/CTA. The extraocular muscles are also well-evaluated with coronal MRI of the orbits.

C. Chemosis and proptosis. Carotid-cavernous fistulae (CCFs) are the most common causes of ophthalmic venous system flow reversal and engorgement. Direct CCFs are caused by arterial wall rupture of the intracavernous carotid segment, most commonly from a traumatic arterial laceration, less commonly from spontaneous rupture of a small aneurysm, Ehlers–Danlos' syndrome type IV (vascular type), fibromuscular dysplasia, or a spontaneous arterial dissection. Indirect CCFs are because of spontaneous arteriovenous shunting to the ophthalmic vein from dural arterial branches of the external carotid. The most common associations being pregnancy, dehydration, and sinus infections. Contrast-enhanced CT and MRI show dilated ophthalmic vein and cavernous sinus in direct CCFs. Indirect CCFs may be much more subtle, sometimes only suspected on the basis of small flow voids around a dural sinus. Catheter angiography is diagnostic and provides the route for transvascular therapy.

X. NECK PAIN AND CERVICAL RADICULOPATHY

Cervical spondylosis is the most common cause of neck pain and cervical radiculopathy, and its incidence increases with age. It is characterized by hypertrophic arthropathy of the facet joints, osteophyte formation at the disk margins, and progressive intervertebral disk degeneration and herniation. All these changes result in central canal and neural foraminal stenoses, with resulting restriction of the spinal cord and the nerve roots. In younger patients, sudden disc herniation may cause acute symptoms. Other causes of cervical pain and radiculopathy include syringomyelia with or without Chiari's malformation, benign tumors of the spinal canal or the neural foramina like schwannomas and meningiomas, demyelinating disease, and post-traumatic myelomalacia. MRI is the preferred method to image these patients because it allows superior evaluation of the cervicomedullary junction, the cord, the spinal canal, and the neural foramina. CT myelography may be useful in patients with cervical spondylosis and contraindications or intolerance to MRI (Fig. 32.8A and B).

XI. BACK PAIN

Low back pain is one of the most common presenting complaints to physicians with up to 85% of the population having experienced symptoms at least once.

A. General causes and evaluation. Most causes of transient low back pain are benign and related to degenerative disease, muscle strain, mild trauma, excess weight, and poor posture. There is a widely held perception in both the medical community and the public is that imaging for back pain is overutilized. Imaging is recommended for back pain associated with certain findings, including radiculopathy or lower motor neuron deficit, sudden onset, older age, signs of systemic infection, known or suspected malignancy, and trauma. MRI is the preferred study in these cases. The relationship between persistent back pains including radicular pain may be striking. Instability may be defined as loss of support of a segment of the spine, subjecting it to abnormal displacement during physiologic movements. Plain X-rays of the spine, in neutral position, flexion, and extension are the most widely used screening method and allow identification of patients who are

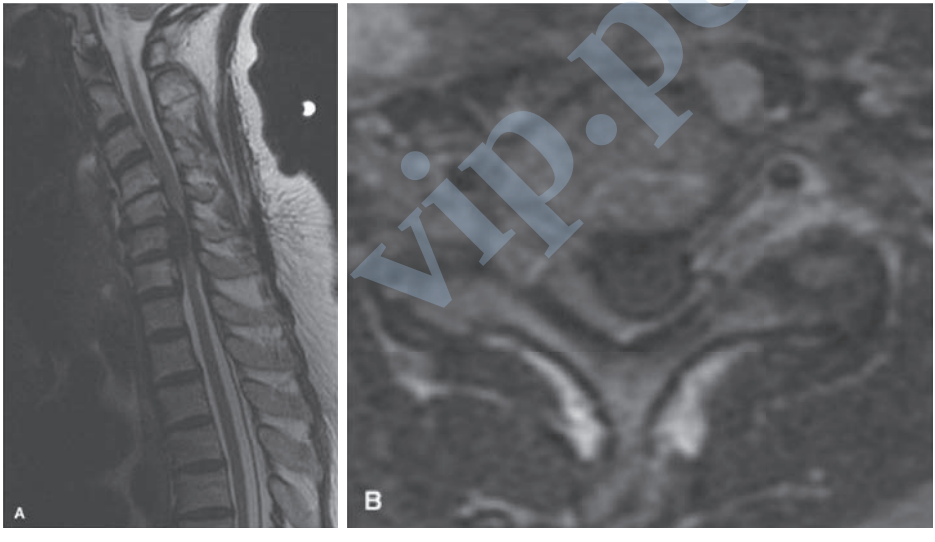

FIGURE 32.8 T2 sagittal image **(A)** and axial image **(B)** demonstrate a large left paracentral disc protrusion at the C5-6 level with marked deformity of the underlying cord with increased signal in the cord that may represent edema or myelomalacia.

likely to benefit from corrective surgery, that is, those with spondylolisthesis and lumbar intervertebral instability. CT may be useful to provide further detail.

B. Lumbar radiculopathy (sciatica). It is pain that originates along the course of the sciatic nerve, which runs from the lumbar spine to the posterior thigh. Lumbar disc herniation, the most common cause of sciatica, is a break in the annulus fibrosus with subsequent displacement of nucleus pulposus, cartilage, or bone beyond the disc space. Other causes of sciatica include degenerative disease (including synovial cysts) and spinal stenosis, tumors (primary and metastatic), infections (osteomyelitis and abscess), and hematomas (epidural, subdural, and psoas). MRI is the study of choice for the initial evaluation of lumbar radiculopathy, as it demonstrates the conus, cauda equina, nerve roots, bony elements, and discs with exquisite contrast in multiple planes. Contrast enhancement is utilized in evaluating infections and tumors. Disc herniations are well-evaluated with MRI, although CT myelography may allow greater detail of bone abnormalities. MRI is inferior to CT in spondylolysis and spondylolisthesis.

XII. MYELOPATHIES

MRI is the preferred imaging method in myelopathies, both acute and chronic, providing multiplanar imaging, superior contrast between normal and abnormal spinal cord, CSF,

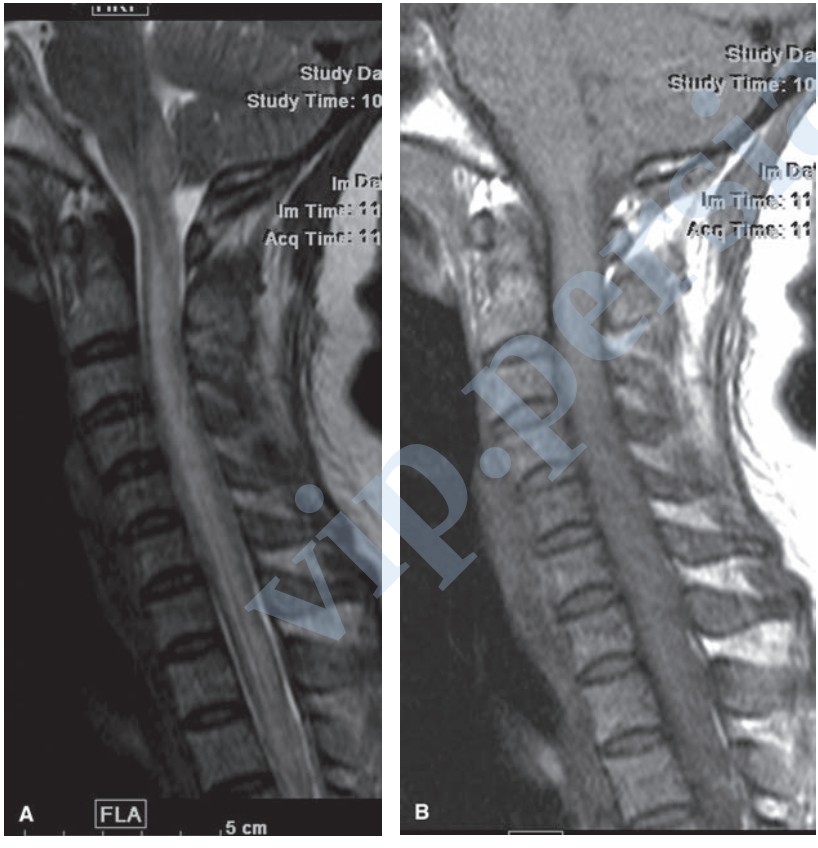

FIGURE 32.9 T2 sagittal **(A)** T1 sagittal **(B),** T1 sagittal with contrast **(C)** and T2 axial **(D)** of the cervical spine demonstrate increased signal on T2 with slight cord enlargement. Post contrast T1 sagittal images demonstrate enhancement in the areas of signal abnormality in this 42-year-old woman with Devic's disease.

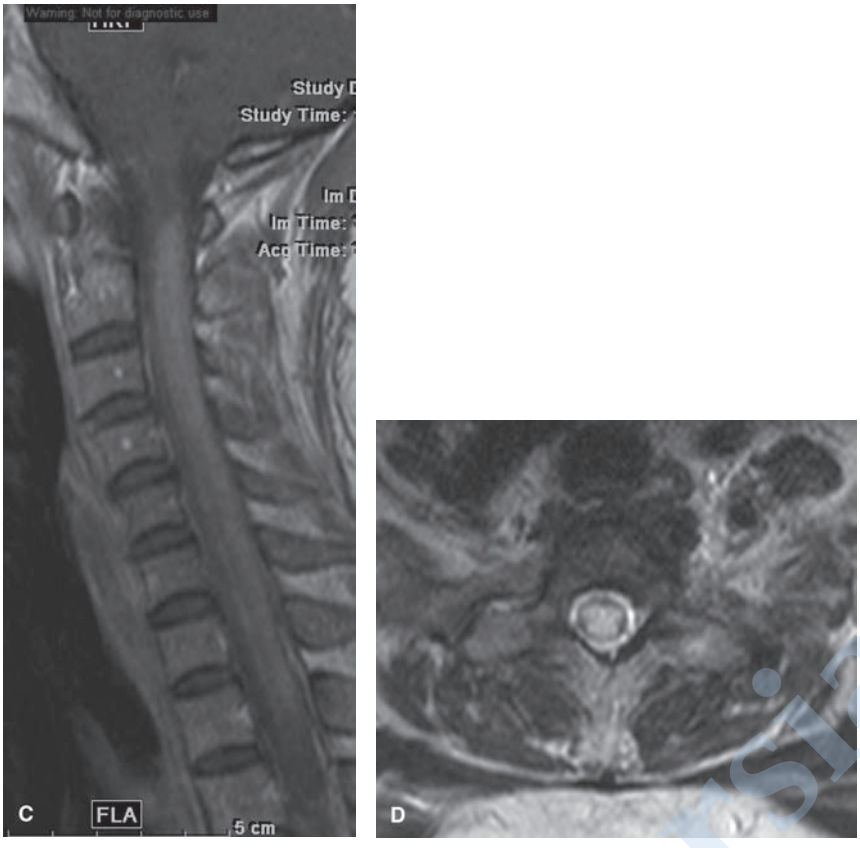

FIGURE 32.9 *Continued*.

fat and bony structures. Gating techniques help reduce artifacts from breathing and CSF, cardiac and vascular pulsations. Patients with acute myelopathy and major contraindications to MRI (pacemakers) may be evaluated with plain CT or CT myelography.

Nontraumatic acute myelopathy most often results from spinal cord compression by a retropulsed neoplastic vertebral compression fracture, usually in an elderly patient with an unknown (or known) cancer, best evaluated by noncontrast whole spine MRI. Acute inflammatory myelopathy caused by transverse myelitis or demyelinating conditions are also best evaluated with MRI, with the addition of contrast (Fig. 32.9A–D). Less commonly, acute myelopathy is caused by spontaneous epidural. **Traumatic cord contusions** are best evaluated by MRI using T2, STIR, and gradient echo sequences.

Causes of **chronic myelopathy** include spinal cord tumors, degenerative disease and disc herniations, syringomyelia, congenital anomalies, inflammatory and demyelinating disease, and spinal dural arteriovenous fistulae. Initial evaluation of these patients is also best undertaken with pre- and postcontrast MRI. CT myelography should be reserved for the rare patient with a major contraindication to MRI.

Recommended Readings

Brazis PW, Masdeu JC, Biller J. *Localization in Clinical Neurology*. 6th ed. Philadelphia, PA: Wolters Kluwer Lippincott Williams & Wilkins; 2011.

Grossman RI, Yousem DM. *Neuroradiology: The Requisites*. 3rd ed. St Louis, MO: Mosby; 2010.

Osborn AG, Salzman KL, Barkovich AJ. *Diagnostic Imaging: Brain*. 2nd ed. Philadelphia, PA: Wolters Kluwer Lippincott Williams & Wilkins; 2009.

CHAPTER 33

Approach to the Selection of Electrodiagnostic, CSF, and Other Ancillary Testing

Paul W. Brazis, Maria Baldwin, and Matthew A. McCoyd

Neurophysiologic electrodiagnostic studies define alterations in the functions of the nervous system that may not be visualized by imaging procedures. The major areas of study include EEG, nerve conduction studies (NCS), EMG, and evoked potentials. The clinical usefulness of these examinations is here discussed, followed by brief descriptions of other ancillary neurologic tests such as polysomnography and the multiple sleep latency test, and finally the indications, contraindications, and utility of performing lumbar puncture (LP) for CSF analysis.

I. ELECTROENCEPHALOGRAM

A. Introduction. The EEG involves recording of the spontaneous electrical activity of the brain from the scalp and activity elicited by activation procedures, including sleep, hyperventilation, and photic stimulation. This electrical activity is the summation of both excitatory and inhibitory postsynaptic potentials from cortical neurons aligned perpendicular to the surface. Small metal disks containing conductive gel are attached to the scalp and ear lobes according to a system of measurements and are connected by flexible wires to a recording instrument that amplifies the brain activity about a million times. The EEG is sampled on moving paper or on a computer simultaneously from 16 to 21 pairs of electrodes (derivations) in selected combinations (montages).

B. Normal EEG activity.

1. **EEG rhythms.** The EEG is a composite of several different types of activity, each with characteristic factors of frequency, amplitude, morphology, reactivity, topography, and quantity. The frequency bands of activity are as follows:
   a. **Delta activity** (4 Hz)
   b. **Theta activity** (4 to 8 Hz)
   c. **Alpha activity** (8 to 13 Hz)
   d. **Beta activity** (≥13 Hz)
2. The most characteristic feature of a normal EEG in an adult during relaxed wakefulness is the **alpha rhythm,** which occurs over the posterior regions of the head while the eyes are closed (Fig. 33.1). Judgments of normality for various EEG activities depend on the age and state of alertness of the subject because complex changes in the EEG patterns occur throughout life and patterns evolve when going from wakefulness through different stages of sleep.
3. **Activation procedures** are used to elicit abnormal activities that may not occur spontaneously.
   a. **Hyperventilation** for 3 minutes is most effective for activating generalized seizure activities such as the spike–wave paroxysms of absence (petit mal) seizures. It may less frequently activate focal abnormalities (e.g., slowing) and focal epileptiform activity. It is contraindicated in a patient with cardiac infarction, recent subarachnoid hemorrhage (SAH), or significant pulmonary disease.
   b. **Photic stimulation** consists of repetitive brief flashes of light generated by an electronic apparatus and delivered at frequencies of 1 to 30 Hz. This procedure evokes responses over the occipitoparietal regions (photic driving). The most frequent abnormal response is diffuse paroxysms of spike–wave complexes (photoparoxysmal or photoconvulsive response) that often indicate a seizure propensity.
   c. **Sleep recordings** are most useful for recording paroxysmal abnormalities in patients with epilepsy. Sleep may activate focal or generalized epileptiform activity. Sleep

deprivation on the night before the study may facilitate sleep, and the deprivation itself may activate epileptiform activity.

C. Abnormal EEG activity. Many EEG changes are nonspecific, but some are highly suggestive of specific entities such as epilepsy, herpes encephalitis, and metabolic encephalopathies. In general, neuronal damage or dysfunction is suggested by the presence of **slow waves** (activity in the theta or delta range) in a focal or diffuse location, whereas the presence of **sharp waves** or **spikes** (epileptiform activity) in a focal or diffuse pattern suggests a seizure tendency. Localized slowing is highly sensitive and significant for local neuronal dysfunction or focal brain damage but is quite nonspecific because it cannot distinguish the pathologic type of lesion. Thus, cerebral infarction, tumor, abscess, and trauma may all cause similar focal EEG changes (Fig. 33.2). Diffuse slowing also indicates organic rather than psychiatric disease but again is nonspecific because such slowing may occur with any significant toxic, metabolic, degenerative, or even multifocal disease process. The EEG is also useful in following the courses of patients with altered states of consciousness and may, in certain circumstances, provide prognostic information. Finally, the EEG is important in the determination of brain death.

1. Epilepsy.

a. Some types of interictal EEG patterns are termed *epileptiform* because they have a distinct morphology and occur in a high proportion of EEGs from patients with seizures but rarely in records from asymptomatic patients. Such patterns include sporadic spikes, sharp waves, and spike and slow wave complexes. Not all spike patterns indicate epilepsy; 14- and 6-Hz positive spikes, sporadic sleep spikes, wicket spikes, 6-Hz spike–wave complexes, and the psychomotor variant pattern are all spike patterns that are of no proven clinical significance. Epileptiform discharges are not seizures in themselves. Seizures are electrographically defined as an evolution in frequency, location, or morphology of epileptiform discharges and usually last >10 seconds. An example of an electrographic seizure is demonstrated in Figure 33.3. Interictal findings must always be interpreted with caution because, although certain

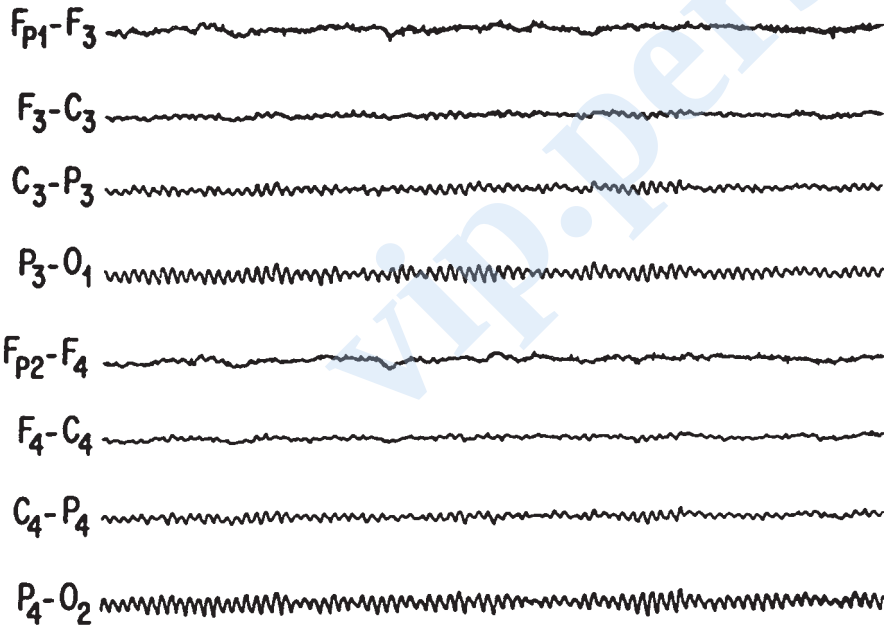

FIGURE 33.1 Normal EEG in an adult man at rest with eyes closed. **Top** four rows—EEG activity from frontal to occipital regions on left. **Bottom** four rows—EEG activity from frontal to occipital regions on right. Note normal alpha activity over posterior head regions.

patterns of abnormality may be evidence useful in supporting a diagnosis of epilepsy, even epileptiform discharges, with few exceptions, are poorly correlated with the frequency and likelihood of recurrence of epileptic seizures. One must always treat the patient and never "treat" the EEG.

b. A substantial portion of patients with unquestioned epilepsy have normal EEGs. However, epileptiform activity has a high correlation with clinical epilepsy. Only about 2% of nonepileptic patients exhibit epileptiform EEG activity, in contrast with 50% to 90% of patients with epilepsy, depending on the circumstances of recording and on whether more than one EEG has been obtained. The most conclusive proof of an epileptic basis for a patient's episodic symptoms is obtained by recording an EEG seizure during a typical behavioral episode.

c. The EEG helps establish whether the seizure originates from a limited or focal area of the brain (**focal or partial seizures**) (Fig. 33.4) or involves the brain as a whole from the onset (**generalized seizures**). This distinction is important because of the different possible causes of these two basic epilepsy types and because the clinical manifestations of both types may be similar.

d. In general, the epileptiform activity on the EEG may be helpful in classifying the patient's seizure type.
   (1) Generalized seizures of nonfocal origin usually are associated with bilaterally synchronous bursts of spikes and spike–wave discharges.
   (2) Consistently the focal epileptiform activity correlates with partial or focal epilepsy.
      (a) Anterior temporal spikes correlate with complex partial seizures.
      (b) Rolandic spikes correlate with simple motor or sensory seizures.
      (c) Occipital spikes correlate with primitive visual hallucinations or diminished visual function.

e. The EEG analysis may permit further discrimination of several relatively **specific electroclinical syndromes.**
   (1) **Hypsarrhythmia** refers to a high-voltage, arrhythmic EEG pattern with a chaotic admixture of continuous, multifocal spike–wave and sharp-wave discharges and widespread, high-voltage, arrhythmic slow waves.

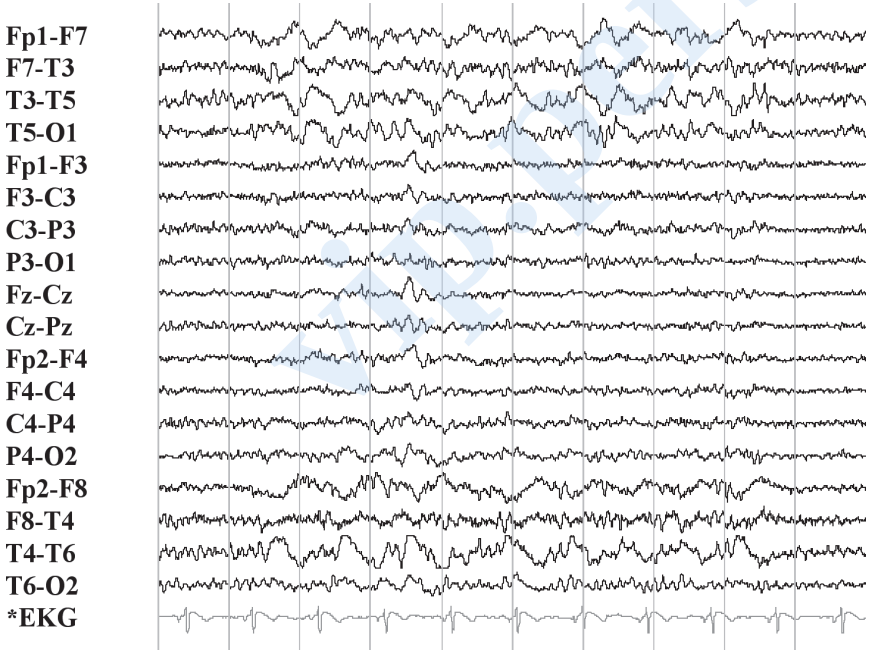

FIGURE 33.2 Left focal fronto-temporal slow wave abnormality in an adult patient with a recent large left fronto-temporal infarction. (Image courtesy of Dr. David Chabolla.)

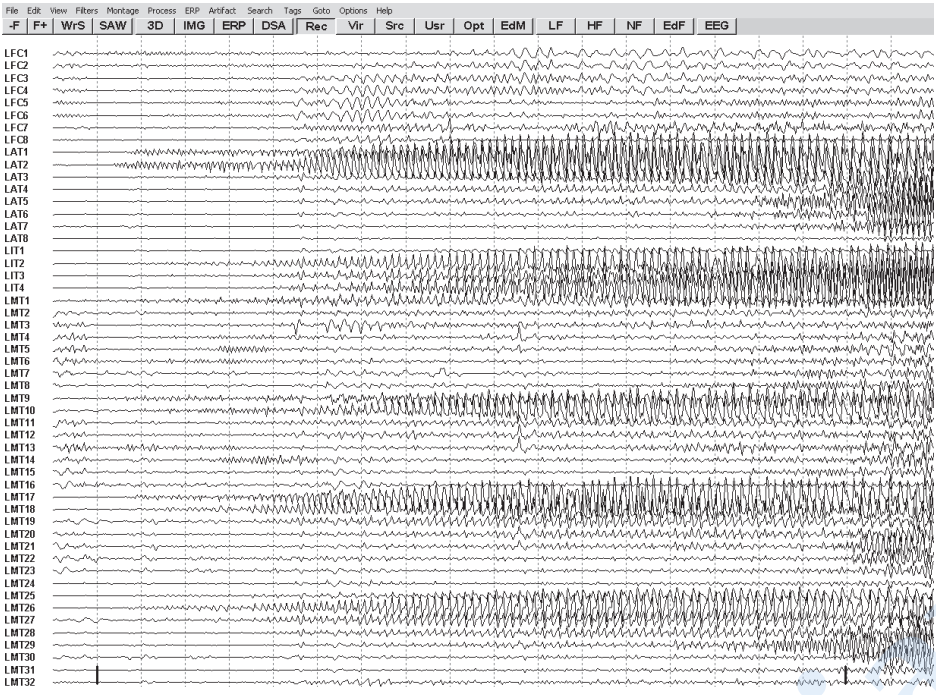

FIGURE 33.3 Focal seizure recorded with intracranial electrodes resting atop cortical surface. Note focal onset of rhythmic discharges, which spread and alter in frequency and morphology. (Image courtesy of Dr. Maria E. Baldwin.)

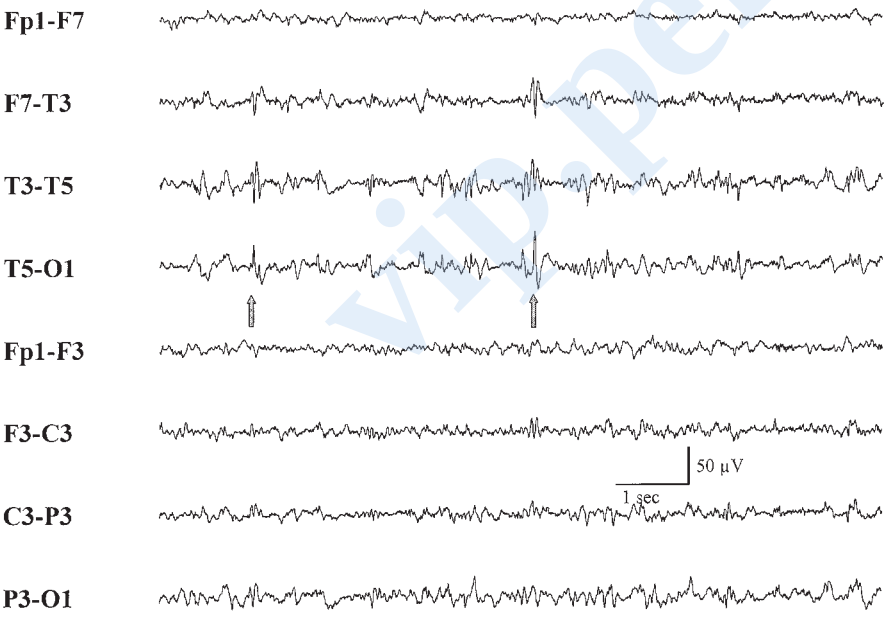

FIGURE 33.4 Focal epileptiform activity (spike) (*arrows*) in left posterior temporal region of an adult with partial seizures.

This infantile EEG pattern usually occurs in association with infantile spasms, myoclonic jerks, and mental retardation (West's syndrome) and usually indicates severe diffuse cerebral dysfunction. **Infantile spasms** consist of tonic flexion or extension of the neck, body, or extremities with the arms flung outward and typically last 3 to 10 seconds. The EEG and clinical findings do not correlate with a specific disease entity but reflect a severe cerebral insult occurring before 1 year of age.

(2) The **3-Hz spike-and-wave activity** is associated with typical absence attacks (**petit mal epilepsy**) (Fig. 33.5). This pattern most often occurs in children between the ages of 3 and 15 years and is enhanced by hyperventilation and hypoglycemia. These bursts are typically accompanied by clinical signs such as staring, brief clonic movements, unresponsiveness, and motor arrest.

(3) **Generalized multiple spikes and waves** (polyspike–wave pattern) are typically associated with myoclonic epilepsy or other generalized epilepsy syndromes (Fig. 33.6).

(4) **Generalized slow spike-and-wave patterns** at a frequency of 1 to 2.5 Hz occur in children between the ages of 1 and 6 years who have some underlying diffuse cerebral dysfunction. Most of these children are mentally retarded and have poorly controlled seizures. The clinical triad of mental retardation, severe seizures, and the slow spike-and-wave pattern is called the **Lennox–Gastaut's syndrome.**

(5) **Central–midtemporal spikes** occur in childhood and are associated with benign rolandic epilepsy. These seizures are often nocturnal and consist of focal clonic movements of the face or hand; tingling in the side of the mouth, tongue, cheek, or hand; motor speech arrest; and excessive salivation. The spells are easily controlled with anticonvulsants and disappear by 12 to 14 years of age.

(6) **Periodic lateralized epileptiform discharges (PLEDs)** are high-voltage, sharply contoured complexes that occur over one cerebral hemisphere with a particular periodicity. These complexes are not necessarily epileptic and usually correlate with acute destructive cerebral lesions, including infarction, rapidly growing tumors, and herpes simplex encephalitis (HSE) (Fig. 33.7). In the past, there was much debate if PLEDs constituted seizure activity. A consensus has now been reached in which PLEDs is not considered an ictal pattern, especially if the discharges occur at slower frequencies of 2 Hz or less.

f. **Focal slowing (delta activity)** in the interictal period usually indicates an underlying structural lesion of the brain as the cause of the seizures. However, such focal slowing may be a transient aftermath of a partial seizure and may not indicate a gross structural lesion. Such slowing may correlate with a clinical transient postictal neurologic deficit (Todd's phenomenon) and subsides within 3 days after the ictus.

g. The EEG can make a critical contribution to the diagnosis of a patient who is obtunded when prolonged subclinical seizures with only brief interruptions are recorded, signifying **nonconvulsive status epilepticus**

h. **Ambulatory EEG monitoring** is the recording of an EEG in a freely mobile patient outside of the EEG laboratory, similar to Holter's monitoring for ECG recording. The main indication is to determine whether a spell is a seizure or some other phenomenon, especially in patients whose spells occur at unusual times or in association with specific events or activities. The yield depends on the type of patient selected, but the absence of EEG seizure activity during a spell does not fully exclude a seizure disorder, because surface electrodes may not record some mesial temporal, basal frontal, or deep midsagittal seizure discharges.

i. Patients with intractable focal seizures are sometimes candidates for surgical removal of the area of abnormality. Precise identification of the epileptogenic brain area requires special inpatient monitoring facilities for simultaneous closed-circuit television (CCTV) and EEG recording. Prolonged CCTV–EEG monitoring is also often used to document whether a patient's clinical spells are epileptic or functional (psychogenic).

2. Altered states of consciousness.

a. For most causes of acute encephalopathy (e.g., toxic–metabolic disease), the EEG changes are nonspecific, consisting of diffuse slowing. There is, however, a generally good correlation between the degree of EEG abnormality and the clinical state.

b. An abnormal EEG confirms an organic rather than a psychogenic cause for a patient's altered state of consciousness. It is also required to document unrecognized epileptic activity as a cause of depressed consciousness (nonconvulsive status epilepticus).
c. **Certain** EEG patterns increase the likelihood of specific metabolic disorders.
   (1) Prominent **generalized fast (beta) activity** in the EEG of a comatose or obtunded patient should raise the suspicion of drug intoxication most commonly seen with benzodiazepines.

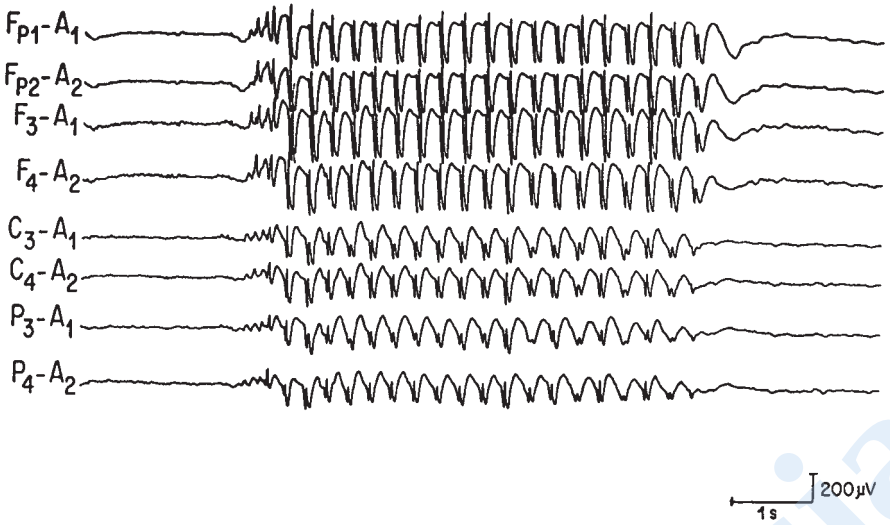

FIGURE 33.5 Burst of generalized 3 per second spike and wave discharges in a child with absence (petit mal) seizures.

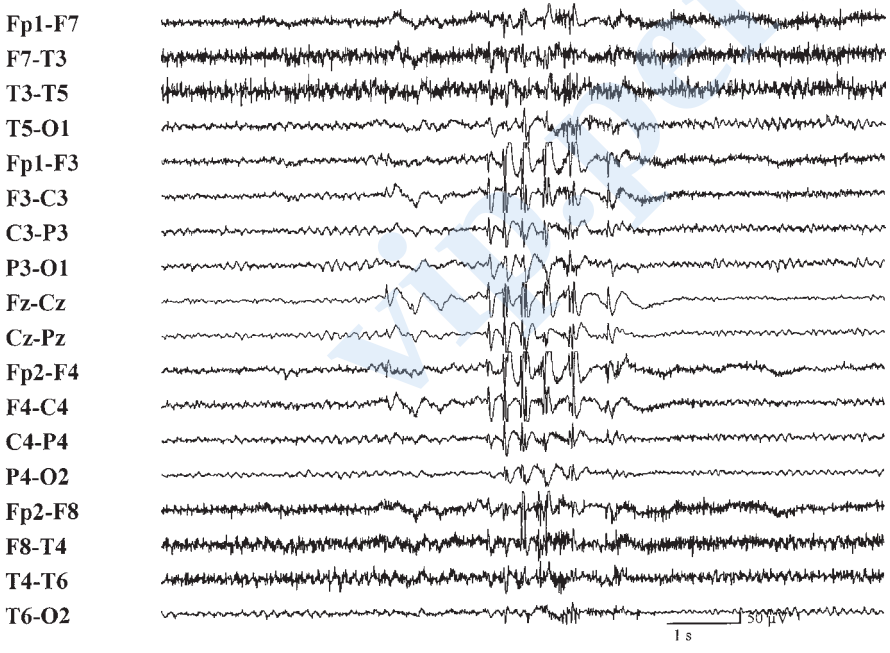

FIGURE 33.6 Burst of generalized multiple spike and wave discharges in a patient with generalized tonic–clonic seizures.

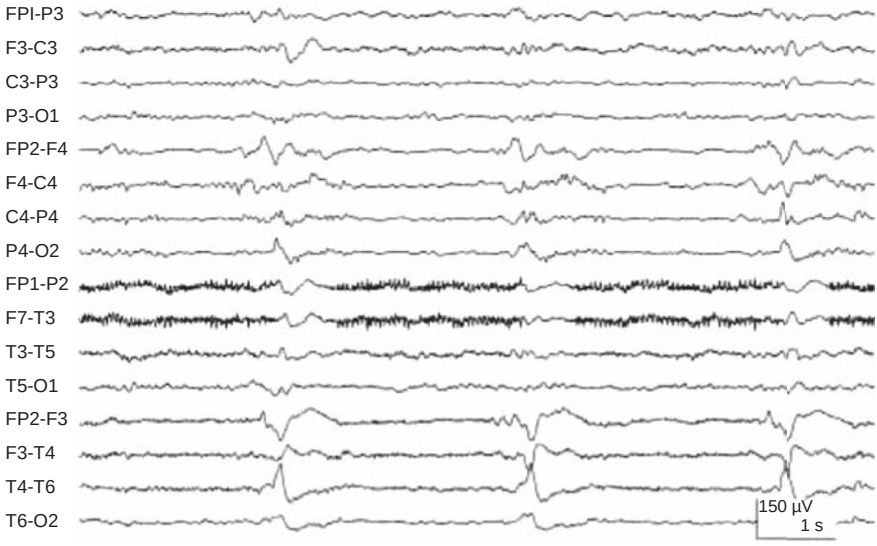

FIGURE 33.7 Right periodic lateralized epileptiform discharges (PLEDs) in a patient with HSE. Compare this figure with that of Figure 33.3 demonstrating a focal seizure. The PLED activity is monotonous and static with little spread and changes in frequency and morphology. In addition, frequency of PLEDs tend to be slower (<2 Hz).

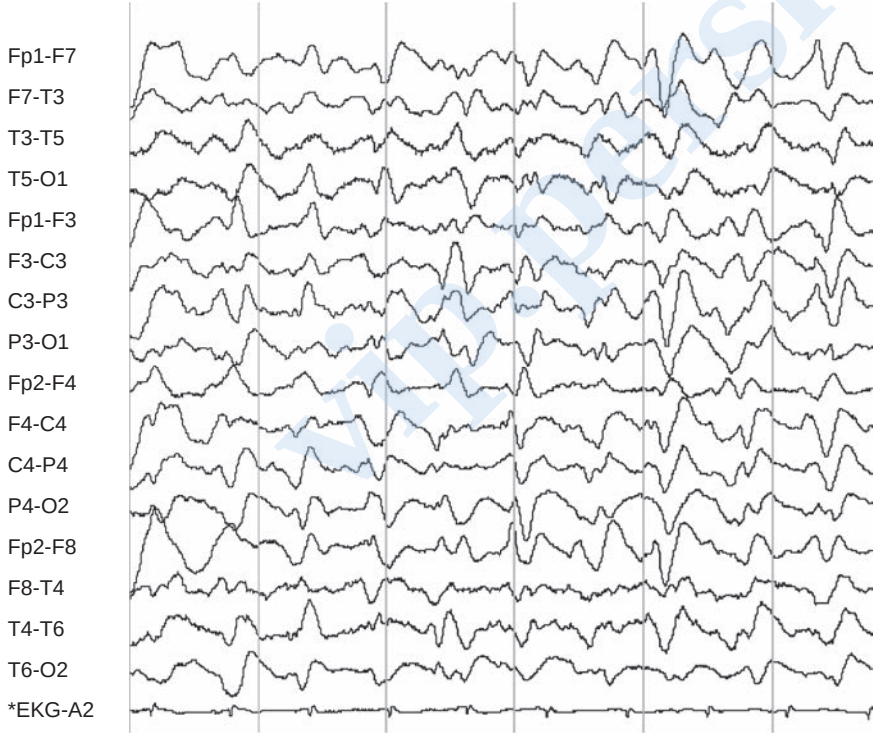

FIGURE 33.8 Frontal predominant triphasic waves and diffuse slow-wave abnormality in a patient with hepatic encephalopathy. (Image courtesy of Dr. David Chabolla.)

(2) Broad **triphasic waves** that are bilaterally symmetric and synchronous and have a frontal predominance may occur during an intermediate stage of hepatic encephalopathy (Fig. 33.8). However, such a pattern may also occur with other metabolic disorders.
(3) Severe generalized voltage depression may suggest hypothyroidism if anoxia and hypothermia can be excluded.
(4) Patients with uremia, uremic patients undergoing hemodialysis, and patients with hyponatremia may exhibit paroxysmal spike–wave discharges and a photoparoxysmal response to photic stimulation in addition to the diffuse slow–wave abnormality.
(5) The focal epileptiform activity is commonly seen in hyperosmolar coma.

d. **Cerebral hypoxia** produces diffuse nonspecific slow-wave abnormalities that may be reversible. More severe hypoxia may cause EEG abnormalities that may be paroxysmal and associated with clinical myoclonus. An EEG obtained 6 hours or more after a hypoxic insult may demonstrate patterns of prognostic value in determining the likelihood of neurologic recovery. A poor neurologic outcome is suggested by the presence of the following abnormalities.
(1) **Alpha coma** refers to the apparent paradoxical appearance of the monorhythmic alpha frequency activity in the EEG of a comatose patient (Fig. 33.9). However, in contrast to normal alpha activity, that observed in alpha coma is generalized, often most prominent frontally, and completely unreactive to external stimuli.
(2) The **burst–suppression pattern** consists of occasional generalized bursts of medium- to high-voltage, mixed-frequency slow-wave activity, sometimes with intermixed spikes, with intervening periods of severe voltage depression or cerebral inactivity. The bursts may be accompanied by generalized myoclonic jerks.
(3) The **periodic pattern** consists of generalized spikes or sharp waves that recur at a relatively fixed periodicity of 1 to 2 per second. The periodic pattern is usually accompanied by myoclonic jerks.
(4) **Electrocerebral silence.** See **I.C.3.a.**

e. **Infectious disease processes** of the CNS produce predominantly diffuse and nonspecific slow-wave activity. However, certain EEG patterns assist in the diagnosis of specific infectious etiologies.
(1) The EEG is extremely important in the initial assessment of **HSE,** often showing abnormalities before lesions detected by CT or MRI are recognized. A majority

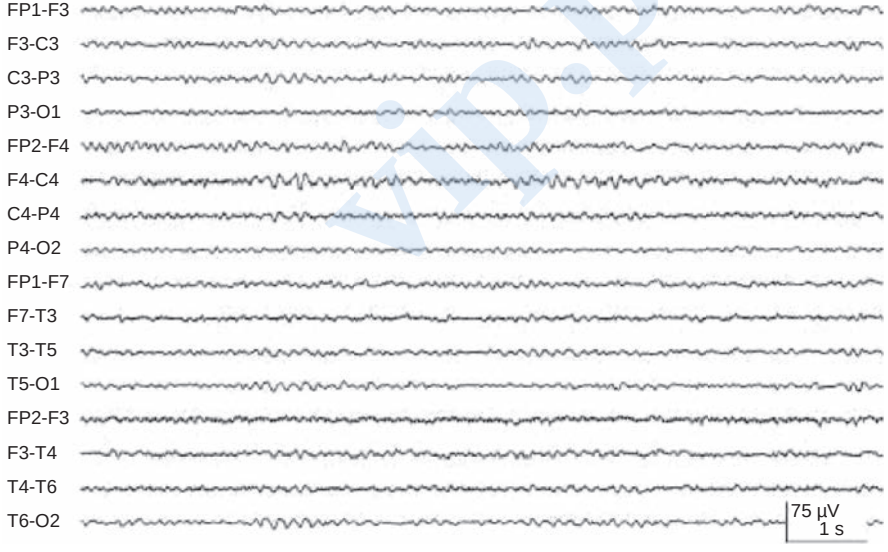

FIGURE 33.9 Alpha coma in an adult patient post cardiorespiratory arrest.

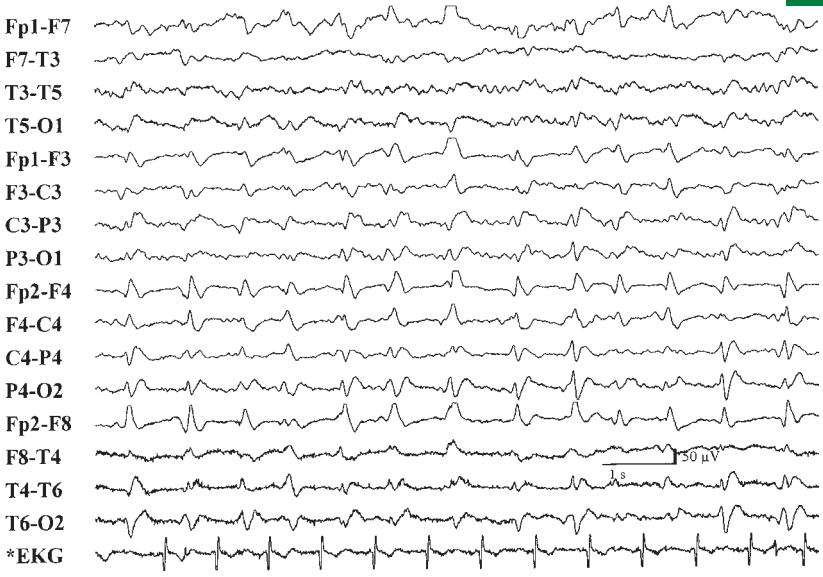

FIGURE 33.10 Generalized periodic (approximately 1 per second) diphasic and triphasic sharp waves seen in patient with biopsy-proven Creutzfeldt–Jakob's disease.

of patients show temporal or frontotemporal slowing that may be unilateral or, if bilateral, asymmetric. **Periodic sharp complexes** over one or both frontotemporal regions add relative specificity to the EEG findings (Fig. 33.7). These diagnostic features usually appear between the 2nd and 15th days of illness and are sometimes detected only on serial tracings.

(2) **Subacute sclerosing panencephalitis (SSPE)** has a distinctive EEG pattern of periodic bursts of stereotyped slow-wave and sharp-wave complexes occurring at intervals of 3 to 15 seconds.

(3) **Transmissible spongiform encephalopathy** is associated with a relatively specific EEG pattern of diffuse high-voltage diphasic and triphasic sharp-wave complexes occurring at a periodicity of approximately 1 per second (Fig. 33.10). This periodic pattern is noted only in the end state of the disease process. Myoclonic jerks are also frequently seen and can correlate with the periodic discharges.

3. Brain death.

a. Because the EEG is a measure of cerebral—especially cortical—function, it has been widely used to provide objective evidence of loss of that function. With cortical death, the EEG demonstrates complete loss of brain-generated activity—**electrocerebral silence** The determination of electrocerebral silence is technically demanding and requires strict adherence to a standard special recording protocol.

b. Rarely, temporary and reversible loss of cerebral electrical activity may be observed immediately following cardiorespiratory arrest, overdose of CNS depressants, and severe hypothermia. Therefore, electrocerebral silence in these circumstances does not indicate irreversible cortical dysfunction.

c. Patients in a chronic vegetative state with preserved brainstem function may have an isoelectric EEG, probably reflecting total neocortical death.

d. Thus, the establishment of **brain death** (cerebral plus brainstem death) requires the following criteria.

(1) Irreversible structural brain damage.
(2) Apneic coma.
(3) Loss of brainstem reflexes and signs of brainstem function.
(4) Electrocerebral silence on EEG (best viewed as a confirmatory test).

II. NERVE CONDUCTION STUDIES AND THE ELECTROMYOGRAM

A. Introduction.

1. **NCS** comprise a simple and reliable method of testing peripheral nerve function. An impulse initiated by electrical stimulation of the nerve travels along motor, sensory, or mixed nerves, and the conduction characteristics of the impulse are assessed by recording potentials either from the muscle innervated by the motor nerve or from the nerve itself.
2. The **motor unit** consists of a single-lower motor neuron and all of the muscle fibers it innervates. **Motor NCS** are techniques used to assess the integrity of the motor unit. Information about the function and the structural status of the motor neuron, nerve, neuromuscular junction, and muscle is acquired. Quantitative information can be obtained regarding the location, distribution, time course, and pathophysiology of lesions affecting the peripheral nervous system (PNS). Prognosis, response to treatment, and the status of repair of the motor unit may also be obtained. For motor conduction studies, recording electrodes are placed on the skin over the motor point of a muscle and over the tendon of the muscle, and stimulating electrodes are placed over the skin along the course of the nerve to be tested. The response of the muscle to electrical stimulation can be measured by recording the compound muscle action potential (CMAP), which is the summation of the electrical potentials of all muscle fibers that respond to the stimulation of the nerve (Fig. 33.11). The time it takes for the electrical impulse to travel to the muscle (latency) can be measured, and by stimulating the nerve at various locations and measuring the distance the stimulus travels, motor nerve conduction velocities are attained. Motor NCS can be used for the following purposes.

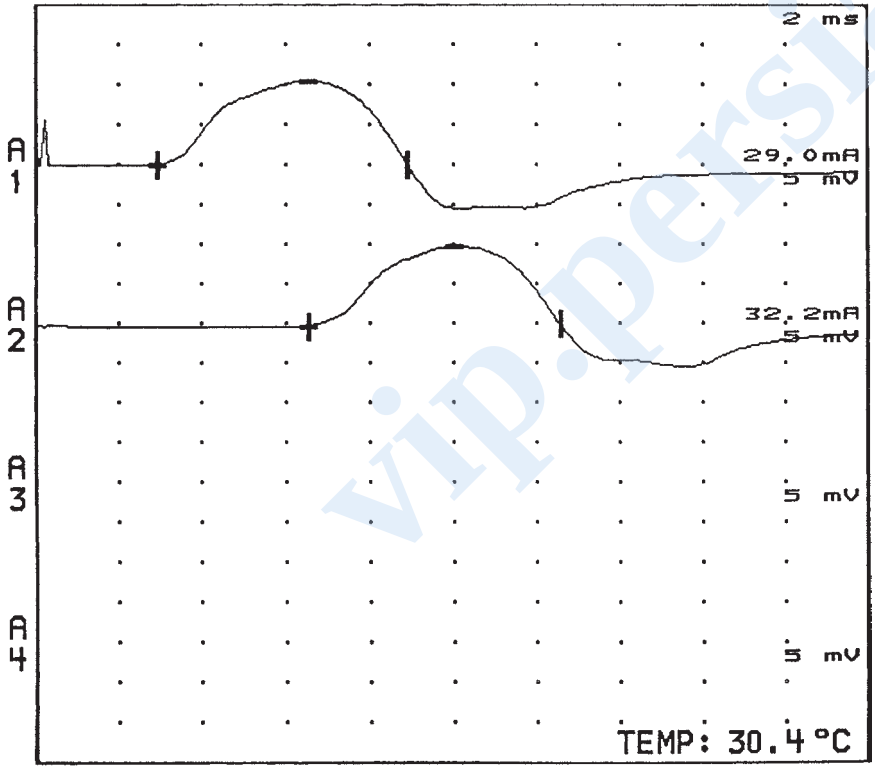

FIGURE 33.11 Compound muscle action potentials recorded from the thenar muscles with stimulation of the left median nerve at the wrist (*upper potential at A1*) and forearm (*lower potential at A2*).

a. To obtain objective evidence of disease of motor units.
b. To identify and localize sites of compression, ischemia, and other focal lesions of nerves that can be manifested by conduction block, slowed conduction at the site of the lesion, or abnormal conduction proximal or distal to the lesion.
c. To detect widespread subclinical involvement of nerves in patients who present with clinical involvement of a single nerve (i.e., mononeuropathies).
d. To differentiate peripheral neuropathies from lower-motor neuronopathies (e.g., amyotrophic lateral sclerosis) from myopathies in patients with weakness.
e. To detect disease prior to the development of significant clinical signs (e.g., familial neuropathies).

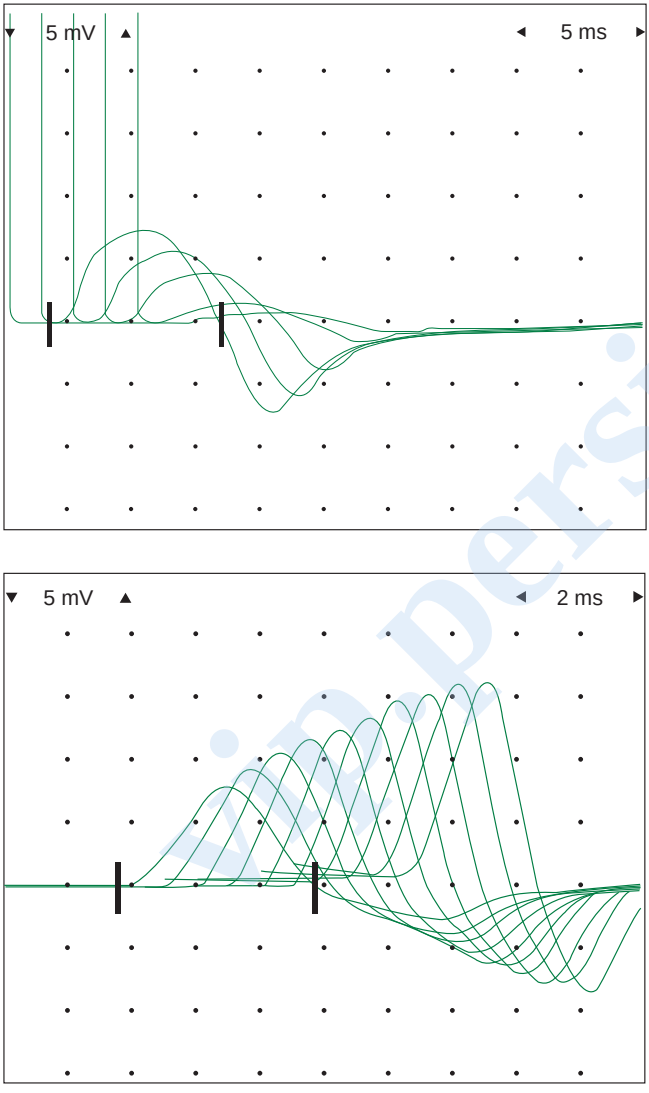

FIGURE 33.12 Decremental response to repetitive stimulation in a patient with generalized myasthenia gravis. **Top:** Decremental response with ulnar nerve stimulation. **Bottom:** Facilitation of compound muscle action potential amplitude with high-frequency stimulation, which can be seen in presynaptic disorders of neuromuscular transmission (this specific patient was positive for a P/Q-calcium channel antibody).

3. Diseases of the neuromuscular junction (e.g., myasthenia gravis [MG], Lambet–Eaton's myasthenic syndrome) can be assessed by **repetitive stimulation of motor nerves.** With postsynaptic fatigability of the neuromuscular junction, if a CMAP is recorded and compared with subsequent CMAPs, a decline in the amplitude of the potential may be observed as progressively fewer muscle fibers respond to the stimuli, even though the nerve is stimulated at rates that a normal muscle could endure for long periods (Fig. 33.12). The hallmark of presynaptic disorders is a significant facilitation of CMAP amplitudes with high-frequency repetitive stimulation.
4. **Sensory NCS** are obtained by recording the action potential evoked in a cutaneous nerve by electrical stimulation (Fig. 33.13). Selective sensory NCS can be performed by stimulating nerves that have only sensory components (e.g., the sural nerve) or, alternatively, by selectively stimulating only the sensory components of a mixed nerve. The latter can be done by isolating the sensory components anatomically (i.e., stimulating the digits of the hand and recording over the mixed nerve at the wrist or elbow) or stimulating the mixed nerve and recording over the digits where only sensory axons are present for the most part. Sensory NCS may be valuable for the following purposes.
   a. In diffuse disorders affecting the sensory system, for determining which population of sensory nerves is involved (e.g., small fibers carrying pain and temperature sensation or large fibers conveying proprioception), determining whether the disorder is predominantly affecting the axon or the myelin of the peripheral nerve, or determining whether the peripheral sensory nerves are involved at all.
   b. In focal neuropathies, for demonstrating a site of injury or block, particularly when only sensory nerves are affected.

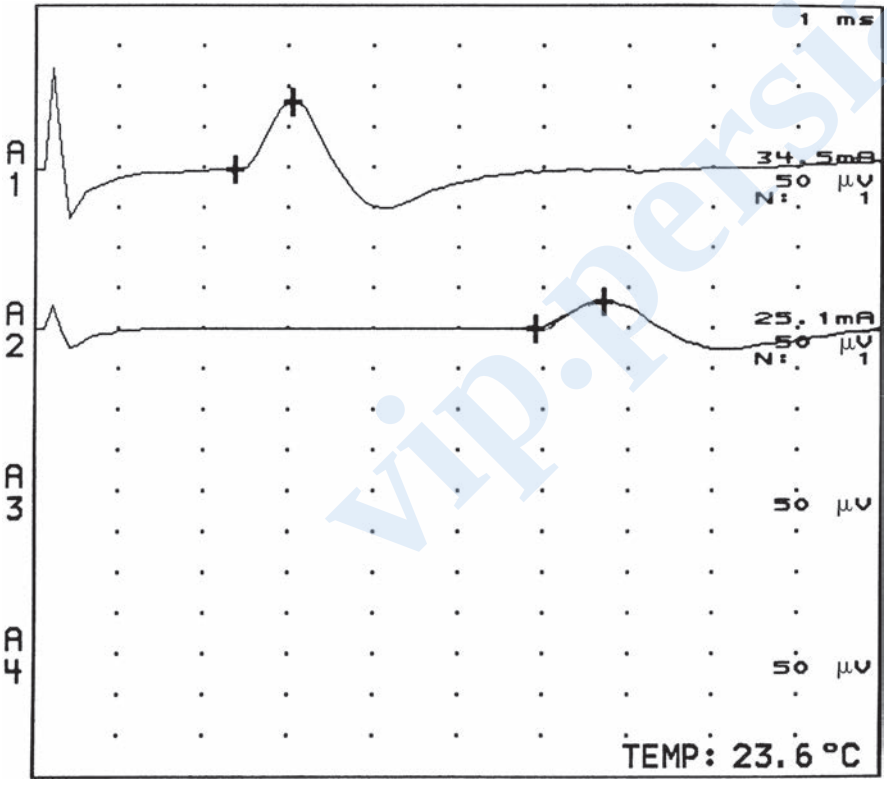

FIGURE 33.13 Sensory nerve action potentials obtained while recording over the index finger with stimulation of the left median nerve at the wrist *(upper response at A1)* and forearm *(lower response at A2)*.

c. For confirmation or quantification when sensory abnormalities appear than motor changes in peripheral neuropathies or before objective clinical signs.
d. For predicting whether a lesion is proximal or distal to the dorsal root (e.g., for differentiating brachial plexus from nerve root injury).
e. For determining disease of the dorsal root ganglion.

5. The **EMG** is usually performed along with NCS and yields complementary information. A needle electrode is inserted into the muscles of interest and the action potentials generated by groups of muscle fibers (the **motor unit potentials** or **MUPs**) are observed and recorded (Fig. 33.14). The muscle is tested at rest, with slight contraction, and with stronger contraction. Normally, the muscle is silent at rest. In **active neuropathic processes**, as well as in severe or inflammatory myopathies, spontaneous action potentials from single-muscle fibers (fibrillation potentials) may occur (Fig. 33.15). In certain neurogenic processes, especially motor neuron disease and diseases of the proximal root, spontaneous contractions of a single-motor unit (fasciculation potentials) may be observed. Characteristic changes in MUP parameters and recruitment may occur in neurogenic or myopathic processes. In **neuropathic conditions**, the MUPs are often of increased amplitude, duration, and degree of polyphasia with reduced recruitment of fibers with increased effort, whereas in **myopathic processes**, the MUPs may be of decreased amplitude and duration with increased polyphasia and rapid (early) recruitment. Single-muscle fiber action potentials may be studied by a technically more difficult method, **single-fiber electromyography** (which is typically used to assess disease of the neuromuscular junction but can be abnormal in neuropathic and myopathic processes).
6. In general, EMG and NCS are used to study and diagnose patients with motor neuron disease (e.g., amyotrophic lateral sclerosis), processes affecting the plexi or nerve roots, entrapment neuropathies, peripheral polyneuropathies, diseases of the neuromuscular junction (e.g., MG), and diseases of the muscle. Because it involves electrical shocks and the insertion of needles into multiple muscles, the EMG/NCS study is uncomfortable. The study is safe as long as electrical safety techniques are applied; a bleeding tendency may limit the EMG study.

B. EMG/NCS abnormalities.

1. The EMG/NCS study is essential for evaluation and electrophysiologic diagnosis of **motor neuron disease** (e.g., amyotrophic lateral sclerosis). In general, NCS are normal except perhaps for some decrease in the CMAP amplitudes (because the disease is purely motor, sensory conduction studies are normal). Needle EMG shows diffuse evidence of neurogenic damage from anterior horn cell injury, including abnormal spontaneous activity (fibrillations and fasciculations), abnormal MUP parameters (large, wide, and polyphasic MUPs), and poor recruitment of MUPs with effort. Often the EMG study indicates active neurogenic damage even in muscles or limbs that appear to have little or no clinical involvement. The needle exam may also provide information about prognosis, and the EMG may assist in the diagnosis of other diseases of the anterior horn cells such as the postpolio syndrome and the spinal muscular atrophies.

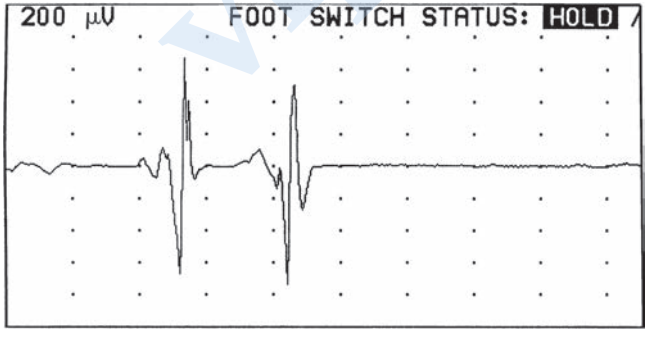

FIGURE 33.14 Motor unit potentials recorded with needle insertion into the right biceps muscle during minimal muscle contraction.

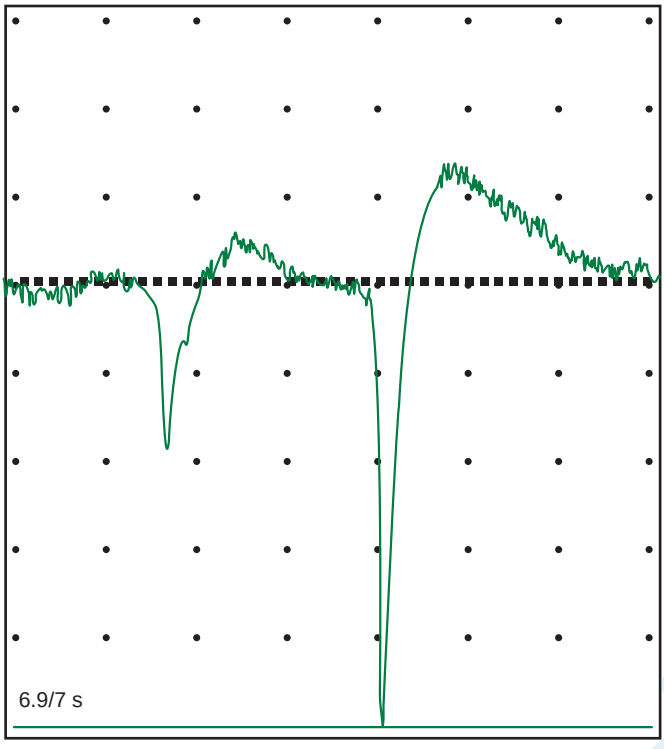

FIGURE 33.15 Positive sharp waves in the extensor hallucis longus muscle.

2. **Radiculopathies** comprise a constellation of symptoms and signs resulting from transient or permanent damage of the nerve at the anatomic level where the nerve exits the spinal canal in the spinal foramina. NCS are generally normal. The EMG shows evidence of neurogenic changes (e.g., fibrillations and MUP changes) in muscles innervated by a specific root, with other muscles innervated by uninvolved roots being spared. The pattern of neurogenic changes depends on the severity of the process, the duration of the disease, and the degree of neurogenic repair (reinnervation). The EMG study can be helpful in several ways, as follows.
   a. It is useful for confirming disease of the nerve root. In studies of patients with surgically demonstrated cervical or lumbosacral radiculopathies, the EMG is abnormal only about 90% of the time. Thus, a normal study does not preclude the presence of a radiculopathy.
   b. It provides further localization by determining which root or roots are affected.
   c. It is useful in determining whether there is active denervation (indicated by the presence of fibrillation potentials).
   d. It can determine the time elapsed since the onset of the radiculopathy (whether it is acute, subacute, chronic, or old).
   e. It may give some information about the severity of the radiculopathy.
   f. It may reveal other abnormalities that explain the patient's symptoms.
   g. It may help to determine if an abnormality on an MRI scan or myelogram has any physiologic significance.
3. Brachial and lumbosacral **plexopathies** and **entrapment neuropathies** (e.g., carpal tunnel syndrome, ulnar neuropathies at the elbow, and peroneal neuropathies at the fibular head) are localized and diagnosed with EMG/NCS.
4. **Peripheral polyneuropathies** are often investigated by EMG/NCS. The electrophysiologic characteristics of the neuropathic disorder serve as additional sources of

information to help characterize the disease and allow a narrowing of the differential diagnostic possibilities. EMG/NCS allows evaluation of the amount of motor and sensory involvement, determines whether the lesion is primarily the result of damage to the myelin sheath or to the axon, indicates whether the lesion is focal or diffuse, determines whether the process is distal or proximal, and gives information concerning the severity and temporal profile of the process. Prolonged distal sensory and motor latencies, slowed conduction velocities, abnormalities of sensory responses and MUPs, and "neurogenic" EMG changes occur. When abnormal, the study confirms the presence of a neuropathy, but it should be noted that small fiber sensory neuropathies (i.e., those affecting only sensory nerve fibers conveying pain and temperature sensation) are often associated with normal studies. EMG/NCS can separate a generalized sensorimotor peripheral polyneuropathy from multiple mononeuropathies at sites of common compression (e.g., median and ulnar neuropathies at the wrist). Peripheral polyneuropathies may be divided by electrophysiologic patterns into the following categories:

a. Uniform demyelinating mixed sensorimotor neuropathies, including certain hereditary neuropathies (Fig. 33.16), metachromatic leukodystrophy, Krabbe's disease, and Tangier disease.

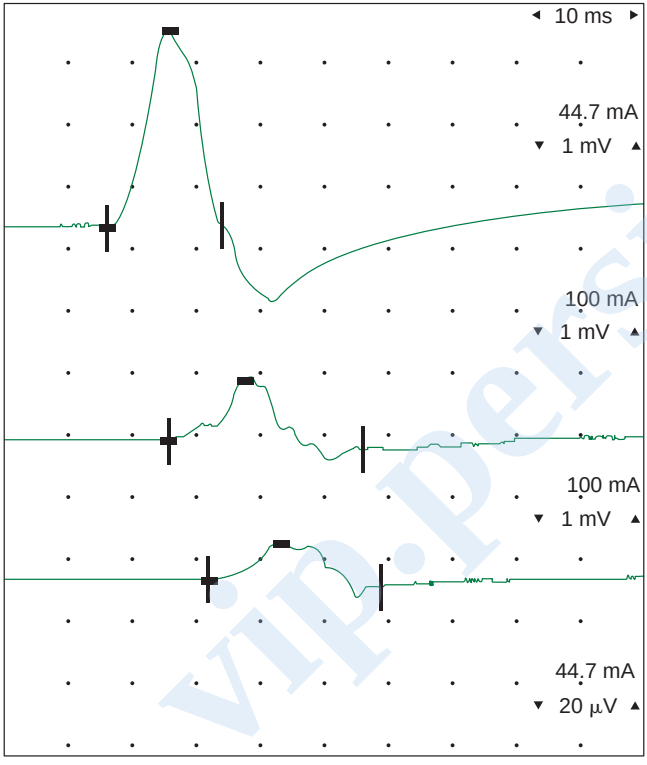

FIGURE 33.16 Motor nerve conduction studies demonstrating uniform demyelination of the peripheral nerve in a patient with hereditary motor neuropathy (Charcot–Marie–Tooth's disease type 1a, CMT). The compound muscle action potential (CMAP) amplitude is relatively preserved on proximal as compared with distal nerve stimulation. A diffusely and homogeneously demyelinating process, such as CMT type 1a will demonstrate relatively preserved CMAP configurations with prolonged latencies and slowed conduction velocities. A nonuniform, segmental demyelinating process (such as acute inflammatory demyelinating peripheral polyneuropathy, that is, Guillain–Barré's syndrome) may demonstrate conduction block and variable slowing within the same nerve trunk, resulting in CMAPs with reduced amplitude and dispersed configuration at proximal sites of stimulation (**bottom** image).

b. Segmental demyelinating motor sensory polyneuropathies, including inflammatory neuropathies (e.g., Guillain–Barré's syndrome, chronic inflammatory demyelinating polyneuropathy) and neuropathies associated with gammopathies, hypothyroidism, carcinoma or lymphoma, AIDS, Lyme's disease, and certain toxins.
c. Axonal motor sensory polyneuropathies, including porphyria, certain hereditary neuropathies, lymphomatous neuropathies, and certain toxic neuropathies.
d. Axonal sensory neuronopathy (disease of the dorsal root ganglion) or neuropathies, including certain hereditary neuropathies, primary amyloidosis, Sjögren's syndrome, paraneoplastic neuropathies, and neuropathies caused by drugs, vitamin B_{12} deficiency or antidisialosyl ganglioside antibodies (also referred to as "CANOMAD" syndrome).
e. Mixed axonal demyelinating sensorimotor polyneuropathies resulting from uremia or diabetes mellitus.
f. Axonal sensorimotor polyneuropathies, including neuropathies caused by nutritional deficiencies, monoclonal gammopathies, alcohol, sarcoidosis, connective tissue diseases, toxins, heavy metals, and drugs.

5. **Diseases of the neuromuscular junction** may be diagnosed by repetitive stimulation studies. Repetitive stimulation of motor nerves is used chiefly in the diagnosis of **MG**. In this disease, a characteristic progressive decline in the amplitude of the first few responses to stimulation is revealed at a stimulation rate of 2 per second (Fig. 33.12).

FIGURE 33.17 **Top figure:** Typical chronic neurogenic MUAP changes (reduced recruitment, increased amplitude, and duration). **Bottom figure:** Typical myopathic changes (early recruitment of small, polyphasic units). (Image courtesy of Dr. Matthew McCoyd.)

The defect may be further characterized by the way it is altered after a brief contraction of the muscle. In some MG patients with normal repetitive stimulation studies, the diagnosis may be assisted by single-fiber EMG. Repetitive stimulation studies are also invaluable in the diagnosis of the Lambert–Eaton's myasthenic syndrome. In the myasthenic syndrome, the initial action potential evoked in the rested muscle by a single-maximal nerve stimulation is greatly reduced in amplitude. A further reduction in the amplitude may occur with repetitive stimulation at low rates, but striking facilitation (enlargement of the MUPs of usually >100%) occurs during stimulation at higher rates. Unusual fatigability of the peripheral neuromuscular system may occasionally be demonstrated in other diseases, such as amyotrophic lateral sclerosis, but this abnormality is of little diagnostic value.

6. Electrodiagnostic studies show a wide variety of abnormalities in patients with **myopathies**. The NCS is essentially normal, except for occasional reductions in CMAP amplitudes. The EMG may reveal fibrillation potentials in severe myopathies or in inflammatory myopathies (e.g., polymyositis). "Myopathic" MUPs are of decreased amplitude and duration with increased polyphasia and rapid recruitment out of proportion to the degree of contraction effort (Fig. 33.17). The EMG studies usually are not sufficient to identify a specific disease, but the pattern of findings can be associated with groups of muscle disorders. Toxic and endocrine myopathies may produce little or no EMG abnormalities. An EMG/NCS examination can
   a. distinguish neurogenic from myopathic disorders as causes of weakness,
   b. provide clues to the etiology of a myopathy,
   c. provide estimates of the severity and acuteness of the process,
   d. assess the activity and course of the disease,
   e. provide important information on the distribution of involvement to guide selection of a biopsy site (muscle biopsy must not be performed on a muscle that has been needled but in a corresponding muscle in the opposite extremity), and
   f. detect abnormalities even if not clinically apparent.

III. EVOKED POTENTIALS

A. Introduction. Evoked potentials are electrical signals generated by the nervous system in response to sensory stimuli. The timing and location of these signals are determined by the sensory system involved and the sequence in which different neural structures are activated. Identical sensory stimuli are presented repeatedly while a computer averages the time-locked low-voltage responses from the brain or spinal cord and unrelated electrical noise and background EEG activity are averaged out.

B. Visual evoked potentials (VEPs).

1. Disorders of central visual pathways are tested by VEPs, which are the cortical responses to visual stimuli. Stroboscopic flashes of light or, more commonly, black-and-white checkerboard patterns evoke potentials over the occipital lobes that are detected by scalp electrodes. The major positive deflection at a latency of approximately 100 m (the **P100 response**) (Fig. 33.18) is most useful for clinical applications. Delays in this latency suggest damage to visual conducting pathways.
2. Unilateral prolongation of the P100 response implies an abnormality anterior to the optic chiasm (usually in the optic nerve) on that side. Bilateral P100 delay can be caused by bilateral lesions either anterior or posterior to the chiasm or by a lesion within the chiasm itself.
3. **Uses of VEPs.**
   a. The VEPs may aid in the detection of a clinically "silent" lesion in a patient suspected of having multiple sclerosis (MS). It is a sufficiently sensitive indicator of optic nerve demyelination that it can reveal asymptomatic and clinically undetectable lesions. The VEPs reveal abnormalities in 70% to 80% of patients with definite MS who do not have histories of optic neuritis or visual symptoms. Abnormalities are not specific for MS and may be abnormal in a variety of other diseases, including certain ocular diseases, compressive lesions of the optic nerve, nutritional and toxic

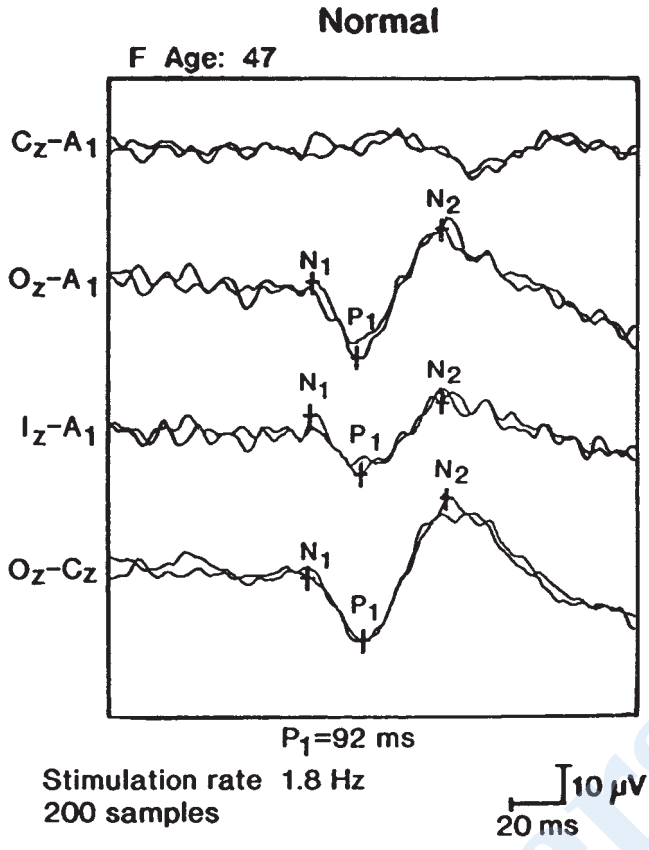

FIGURE 33.18 Full-field visual evoked potential (VEP) in a normal patient. *(P1 = P100 response).*

optic neuropathies, including pernicious anemia, and diffuse CNS diseases such as adrenoleukodystrophy and some spinocerebellar degenerations.

b. The VEP is helpful in distinguishing functional (e.g., psychogenic) visual impairment from true blindness or bilateral optic nerve disease. A normal VEP strongly favors functional illness. It should be mentioned, however, that rare patients have been described with blindness from severe bilateral destruction of the occipital lobes who had essentially normal VEP studies. Also, some patients with functional problems can voluntarily suppress the VEP response by such strategies as transcendental meditation, concentration beyond the plane of the checks, or ocular convergence.

c. The VEPs may be of some assistance in evaluating vision in pediatric patients—for example, in assessing high-risk infants or in the detection of amblyopia.

C. Brainstem auditory evoked potentials (BAEPs).

1. The BAEPs are a series of evoked potentials elicited by auditory clicks and generated by sequential activation of the brainstem auditory pathways. Although five waveforms (I through V) are usually resolved (Fig. 33.19), the most stable and important waveforms are I, III, and V. The I to III interpeak latency is a measure of auditory conduction of the more caudal segment of the brainstem (acoustic nerve to lower pons), whereas the III to V interpeak latency is a measure of conduction in the more rostral pontine and lower midbrain pathways. The I to V interpeak latency is a measure of the total conduction time within the brainstem auditory pathways.
2. Abnormality is measured by prolongation of interpeak latencies, especially asymmetric prolongations, as well as reduction in amplitude or absence of certain waveforms. A prolonged

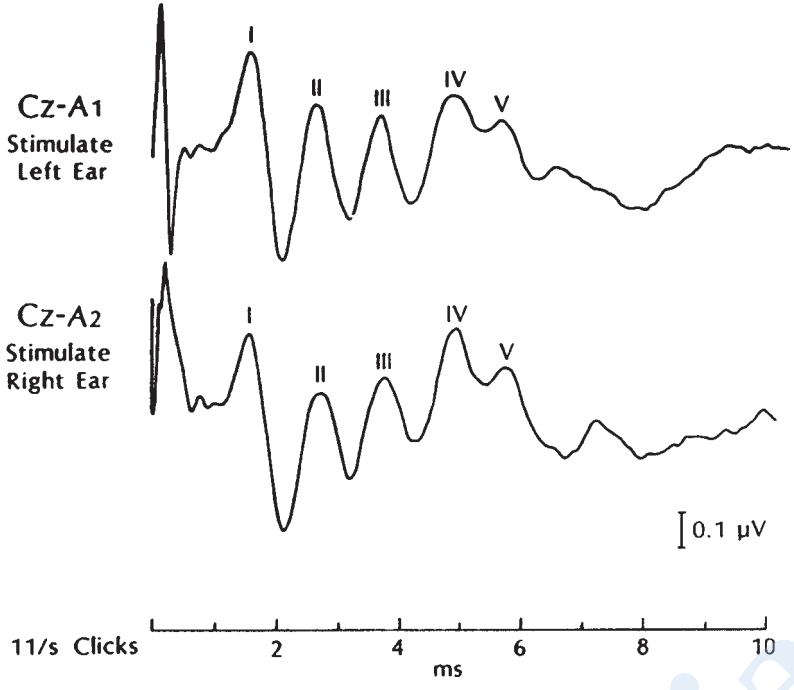

FIGURE 33.19 Brainstem auditory evoked potential study in a normal adult subject. See text for discussion of waveforms.

I to III interpeak latency indicates a lower pontine lesion, whereas a prolonged III to V interpeak latency indicates a lesion of the upper pons–lower midbrain levels.

3. The BAEPs may be clinically helpful in the following circumstances.
   a. The BAEPs, like VEPs, may be very sensitive to white matter disease and may help confirm or document a lesion within the brainstem, even if there are no brainstem signs or symptoms, when MS is suspected clinically and the patient has a lesion outside the brainstem. Approximately 50% of patients with definite MS exhibit abnormal BAEPs. However, VEPs and somatosensory evoked potentials (SEPs) (see **III.D.**) are more sensitive than BAEPs in detecting abnormalities in MS patients. Other demyelinating processes affecting the brainstem, such as central pontine myelinolysis, metachromatic leukodystrophy, and adrenoleukodystrophy, may also cause BAEP abnormalities.
   b. A **posterior fossa tumor** or other mass within or outside of the brainstem can produce abnormal BAEPs by either direct involvement of the brainstem auditory pathways or secondary brainstem compression. The BAEPs are very sensitive screening procedures for acoustic neuromas and other cerebellopontine angle tumors. Monitoring of the BAEPs during such surgeries as acoustic neuroma resections, can provide valuable information to the surgeon and help to preserve hearing.
   c. The BAEPs may assist in the determination of **brain death.** Preservation of wave I with loss of all subsequent response supports brainstem death in the comatose patient. The BAEP does not, however, provide any information about cortical function in the comatose patient.
   d. The BAEPs may be used to assess **hearing in young children** and in patients otherwise unable to cooperate for standard audiometry. The BAEP testing can estimate hearing threshold and may distinguish conductive hearing loss from sensorineural hearing loss.

D. SEPs.

1. Following electrical stimulation of a peripheral nerve (usually the median or ulnar nerve at the wrist or the tibial nerve at the ankle), recording electrodes placed over the spine

and scalp reveal a series of electrical potentials that correspond to sequential activation of neural structures along the dorsal column–lemniscal pathway. These SEPs are named according to their polarities and their times of occurrence in normal individuals. Because SEP latencies vary significantly with body height and limb length, absolute latency values are of limited use; interpeak latencies, which measure the time intervals between successive peaks in the sensory pathways, are incorporated in clinical studies.

2. SEPs yield information concerning PNS abnormalities but are not as effective as standard NCS in identifying and localizing peripheral disorders. Therefore, although SEPs have been used to study plexopathies and radiculopathies, their use is limited for these conditions.
3. **Uses of SEPs.**
   a. SEPs can be used to confirm the presence of a clinically "silent" spinal cord lesion in a patient suspected of having MS. Median SEPs are abnormal in about two-thirds of patients with definite MS; lower-limb SEPs have somewhat greater abnormality rates, probably because of the greater length of white matter traversed. Prolonged central conduction times do not necessarily indicate demyelination because abnormal interpeak latencies may occur with hereditary spastic paraplegia, olivopontocerebellar atrophy, and subacute combined degeneration resulting from vitamin B_{12} deficiency.
   b. Abnormally large (giant) cortical SEPs are characteristic of some relatively rare neurologic conditions, such as progressive myoclonic epilepsy, late infantile ceroid lipofuscinosis, and some other disorders associated with myoclonus.
   c. SEPs may be helpful in demonstrating intact central sensory pathways in patients with functional (e.g., hysterical) sensory loss.
   d. SEPs have been especially helpful in monitoring spinal cord function during surgery (e.g., surgery for correction of spinal scoliosis).

IV. OTHER ANCILLARY NEUROLOGIC STUDIES

A. Polysomnography.

1. Polysomnography consists of continuous monitoring of multiple biologic variables during nocturnal sleep. Eye movements (electrooculography), EEG activity, submental EMG, the ECG, and limb movements are routinely monitored. Respiration is monitored with intraesophageal pressure gauges, intercostal surface EMG, rib cage and abdominal strain gauges, oronasal thermistors or CO_2 detectors, ear or finger oximetry, and other means of determining the presence of central, peripheral, or mixed apnea syndromes. A microphone attached to the throat may detect snoring. Each 30-second epoch of the polysomnogram is scored as awake, stage I to IV non–rapid eye movement (REM) sleep, or REM sleep.
2. Polysomnography is used to investigate two types of problems: sleep complaints (i.e., too much or too little sleep) and risk factors or specific syndromes induced by or linked to sleep or specific sleep states. These disorders include the following:
   a. Sleep apnea syndromes, which may be obstructive, central, or mixed.
   b. Narcolepsy.
   c. Idiopathic CNS hypersomnia.
   d. Periodic movements of sleep and sleep-related myoclonus.
   e. REM behavioral disorder.
   f. Disorders of the sleep–wake cycle.
   g. Parasomnias such as sleepwalking, nightmares, night terrors, and head banging.

B. Multiple sleep latency test.

1. The multiple sleep latency test consists of five 20-minute attempts, once every 2 hours, to fall asleep throughout the day. The aim is to determine the sleep latency and whether or not REM sleep episodes are recorded during the nap. Patients should be withdrawn from sleep-related medications for 10 to 15 days. The study usually follows polysomnography because knowledge of the patient's previous night's sleep is required for appropriate interpretation. During the study, the EEG, submental EMG, ECG, and eye movements are monitored. Normal patients have mean sleep latencies >10 minutes and fewer than two sleep-onset REM periods during the study.

2. The multiple sleep latency test is designed to evaluate the following:
   a. The complaint of **excessive daytime somnolence** by quantifying the time required to fall asleep. Pathologic sleepiness is manifested by a mean sleep latency of <5 minutes.
   b. The possibility of **narcolepsy** by checking for abnormally short latencies to REM sleep. The occurrence of two or more sleep-onset REM periods during the study is strong evidence for narcolepsy, as long as sleep apnea and withdrawal from stimulants and alcohol have been ruled out.

V. LUMBAR PUNCTURE

A. Introduction. An LP should be considered only after a thorough evaluation of the patient and serious consideration of the potential value and hazards of the procedure.

B. Indications for CSF examination and LP are as follows.

1. The CSF examination is a key to the diagnosis and management of various CNS infections, including acute and chronic meningitis and encephalitis. In many patients with fever of unknown origin, even in the absence of meningeal signs, an early LP is commonly of value, especially because meningeal signs may be minimal or absent in very young or elderly patients. Meningeal infection should especially be sought in patients with fever and impaired sensorium or an immunocompromised state (e.g., AIDS patients). If a patient presents with unexplained acute confusion, stupor, or coma, even if afebrile, a CSF examination is necessary for the evaluation of meningoencephalitis. In most clinical settings, a CT scan of the brain or other neuroimaging should be performed before the LP to rule out a possible intracranial mass (e.g., hemorrhage or abscess), which would make LP a potentially lethal procedure. However, in an extremely ill patient in whom acute meningitis, such as meningococcal meningitis, is suspected, treatment should not be delayed while arranging appropriate ancillary testing.
2. In patients with suspected SAH, an urgent CT scan is indicated to evaluate for the presence of blood. However, in approximately 5% to 10% of patients with **SAH**, CT fails to reveal blood, and a spinal tap is indicated. If the diagnostic LP shows subarachnoid blood or xanthochromia, a cerebral angiogram is needed to determine the source of the hemorrhage.
3. In patients with **unexplained dementia,** CSF examination may be necessary to evaluate for CNS vasculitis, infection, or granulomatous disease. The CSF should always be examined in a patient with dementia and a positive fluorescent treponemal antibody absorption study. Also, patients with radiographic hydrocephalus may require a CSF study to exclude chronic meningitis as an etiology for the symptomatic hydrocephalus. In patients with suspected sporadic transmissible spongiform encephalopathy (sTSE), a positive radioimmunoassay of the CSF for "prion protein" (14-3-3 protein) is included in the World Health Organization criterion for "probable sporadic TSE." However, there is some doubt as to the effectiveness of 14-3-3 testing because of false positives, lack of laboratory standardization, and clinical variability of sTSE. Other markers (such as neuron-specific enolase [NSE], tau protein, astrocytic [S100b] proteins and amyloid *ß*) have been investigated. Testing for a combination of factors, timing of testing, and serial studies may increase sensitivity. CSF biomarkers may also be used as an early indicator of Alzheimer's dementia. The combination of a reduced concentration of CSF amyloid *ß*, increased total tau, and increased phospho-tau may be highly sensitive and specific for Alzheimer's disease.
4. CSF examination is usually not warranted and may be dangerous in most patients with stroke. However, CSF analysis may assist in the etiologic diagnosis of **unexplained stroke in young or middle-aged patients** who lack atherosclerotic risk factors. Such etiologies as CNS vasculitis, meningovascular syphilis, and AIDS may be diagnosed. Sustained elevation in CSF biomarkers including NSE and S100b are associated with poor outcome following cardiac arrest.
5. CSF studies may aid in the diagnosis of **MS**, although there is no specific CSF marker for this disease. The CSF WBC counts are typically normal, as are protein and glucose. Elevated CSF IgG levels, with normal serum IgG levels, and the presence of oligoclonal bands in the CSF are considered characteristic for MS. However, CSF analysis for oligoclonal bands was not included in the Revised 2010 "McDonald Criteria" for the

diagnosis of MS. The elevated CSF gamma globulin may also occur in neurosyphilis, viral meningoencephalitis, and SSPE.

6. The CSF analysis can be considered in the evaluation of patients admitted with an **initial tonic–clonic seizure or status epilepticus**, after appropriate neuroimaging, to exclude an active CNS infection or hemorrhage.
7. An LP is necessary to confirm the clinical suspicion of **carcinomatous or leukemic meningitis.** The typical CSF pattern is a pleocytosis with mildly elevated protein, low glucose, and a positive cytology for malignancy. Multiple LPs may be necessary as though cytology has a high specificity (>95%), it carries a low sensitivity (<50%). CSF flow cytometry may help increase the diagnostic yield.
8. CSF studies may aid in the diagnosis of certain **inflammatory or demyelinating neuropathies,** such as the Guillain–Barré's syndrome or chronic idiopathic demyelinating polyradiculoneuropathy. The CSF protein level is often elevated without an abnormal cellular response. The WBC counts >10 per mm^3 should raise suspicion for disorders such as Lyme's disease, sarcoidosis, and HIV.
9. Although an LP is generally contraindicated in patients with papilledema, it is indicated to document increased intracranial pressure in a patient suspected of having **idiopathic intracranial hypertension (pseudotumor cerebri)** after neuroimaging studies have been proven to be normal. The spinal fluid is under increased pressure but is otherwise normal in this entity, except for occasional decreased CSF protein levels. Also, an LP is required to document low-CSF pressure in rare low-pressure syndromes in a patient whose headaches occur on standing and are relieved by lying down.
10. An LP can be used to deliver **intrathecal antibiotics and chemotherapy** in the treatment for certain CNS infections and meningeal malignancies, respectively. Also, it is required in certain diagnostic procedures such as myelography or cisternography.

C. Contraindications for LP.

1. An LP is contraindicated in any patient with **increased intracranial pressure**, except idiopathic intracranial hypertension because of the real danger of cerebral herniation and death.
2. An LP is contraindicated if there is suppuration in the skin or deeper tissues overlying the spinal canal because of the danger of inducing a purulent meningitis.
3. An LP is dangerous in the presence of **anticoagulation therapy or a bleeding diathesis**. Also, heparin should not be reinstituted for a minimum of 2 hours after an LP is performed. In general, an LP is hazardous if the platelet count is below 50,000, or especially if it is below 20,000. In such cases, platelet transfusions should be initiated if possible before the LP.
4. An LP should not be performed when a **spinal mass** is suspected unless the procedure is part of a myelogram with neurosurgical assistance readily available. A dramatic deterioration in spinal cord or cauda equina function can occur after LP.

D. Complications of LP.

1. **Brain herniation and death** may occur if an LP is performed on a patient with an increased intracranial pressure from a cerebral mass lesion. An LP is contraindicated in any patient suspected of having an intracranial mass.
2. **Headache of low-pressure type** may occur in up to 10% of patients after an LP (spinal headache). This type of headache occurs only on standing and is relieved by lying down. It is usually self-limiting but may require an epidural autologous blood patch for relief. Post-LP headache is most common in young women with lower-body mass. Higher-gauge (smaller diameter) needle, needle insertion parallel to dural fibers (bevel up with patient on side), and replacing the stylet prior to needle removal are negatively associated with post-LP headache. The occurrence of post-LP headache is unrelated to CSF opening pressure, cells, and protein; patient position during LP; duration of recumbency after LP; amount of CSF removed; or hydration following LP.
3. **Diplopia**, which usually results from unilateral or bilateral cranial nerve VI palsies, may occur rarely and is usually self-limiting.
4. **Aseptic meningitis** may occur rarely and is characterized by posterior neck pain, headache, and neck stiffness. This process is usually self-limiting.

5. **Spinal epidural, subdural, and subarachnoid hematomas** may occur, especially in patients on anticoagulants or with bleeding diatheses. Such hematomas are usually self-limiting and may cause local pain and meningeal irritation. However, epidural hematoma may rarely cause a flaccid and potentially irreversible paraplegia that requires an emergency surgical evacuation.

E. General comments on the evaluation of LP results.

1. The normal **CSF pressure** is 70 to 180 mm of water in the lateral recumbent position. Pressures should be >200 mm of water to be considered elevated. In an obese patient with possible idiopathic intracranial hypertension, the pressure should be >250 mm of water to establish this diagnosis.
2. The normal **CSF glucose** is approximately two-thirds of the serum glucose level, which must be drawn at the time of the LP. Hypoglycorrhachia (low-CSF glucose) with few white cells suggests a fungal infection, with many white cells a bacterial infection, and with abnormal (malignant) cells a meningeal malignancy.
3. The **CSF protein** may be increased (>100 mg per dl) in many CNS infectious, inflammatory, and malignant processes. Causes of elevated CSF protein with normal neuroimaging studies include myxedema, inflammatory demyelinating polyneuropathies, diabetic polyneuropathy, neurofibromas within the CSF pathways, resolving SAHs, gliomatosis cerebri, CNS vasculitis, and any process that causes spinal compression or obstruction of CSF flow.
4. Normally, the CSF can contain up to five lymphocytes or mononuclear cells per cubic centimeter. A **pleocytosis** causes CSF clouding when there are at least 200 cells per cubic centimeter. An increased WBC count occurs with subarachnoid infections, hemorrhages, chemical meningitis, or meningeal neoplasms. Also, it should be noted that a pleocytosis may occur for approximately 24 hours after a generalized seizure episode.
5. If initial spinal fluid appears bloody, one must attempt to determine whether the source of the blood is a traumatic tap or an SAH. If the initial tube of fluid is bloody and subsequent tubes are progressively clear, it is most likely that the tap was traumatic. One should then immediately centrifuge the fluid to see if the supernatant is clear, which suggests a traumatic tap. If the supernatant fluid is xanthochromic (yellow-tinged), it is likely that the blood has been present in the CSF for a few hours. Xanthochromia occurs approximately several hours after an SAH, reaches its greatest intensity at the end of 1 week, and clears in approximately 2 to 4 weeks. It can also be observed in jaundice and hypercarotenemia.
6. The polymerase chain reaction of the CSF has been found to have great utility in the diagnosis of several CNS infections. These include the following:
   a. Herpes simplex virus I (HSE).
   b. Herpes simplex II (HSE in neonates, recurrent meninigitis).
   c. JC virus (progressive multifocal leukoencephalopathy or PML).
   d. Cytomegalovirus (CMV ependymitis and polyradiculopathy associated with AIDS).
   e. *Borrellia burgdorferi* (Lyme's disease).
   f. *Tropheryma whippelii* (CNS Whipple's disease).
   g. Toxoplasmosis (CNS toxoplasmosis in AIDS).
   h. *Myocobacterium tuberculosis* (TB meningitis).
   i. Other viruses causing encephalitis, including enteroviruses, varicella–zoster virus, Epstein–Barr's virus, West Nile virus, and herpesvirus type 6.

VI. REFERRALS

All clinical neurophysiologic tests should be performed and interpreted by clinicians with expertise and special training in clinical neurophysiology. Laboratories performing these studies must follow the clinical and technical guidelines that have been published by neurophysiologic societies, the American Academy of Neurology, and other organizations. Strict adherence to these guidelines is mandatory to ensure patient safety and meaningful clinical

interpretation. Neurology consultation is suggested whenever LP reveals abnormalities suggesting CNS infection, increased or decreased intracranial pressure, or SAH.

Recommended Readings

Aminoff MJ. *Electrodiagnosis in Clinical Neurology*. 2nd ed. New York, NY: Churchill Livingstone; 1986.

Brenner R, Hirsch L. *Atlas of EEG in Critical Care*. Chichester, UK: John Wiley & Sons; 2010.

Daube JR, ed. *Clinical Neurophysiology*. 2nd ed. New York, NY: Oxford University Press; 2002.

De Meyer G, Shapiro F, Vanderstichele H, et al. Diagnosis-independent Alzheimer's disease biomarker signature in cognitively normal elderly people. *Arch Neurol*. 2010;67(8):949–956.

Donofrio PD, Albers JW. Polyneuropathy: classification by nerve conduction studies and EMG. *Muscle Nerve*. 1990;13:889–903.

DuBois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol*. 2007;6:734–746

DuBois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol*. 2010;9:1118–1127.

Dumitru D, Amato AA, Zwarts MJ. *Electrodiagnostic Medicine*. 2nd ed. Philadelphia, PA: Hanley and Belfus, Inc.; 2002.

Ebersole JS, Pedley TA, eds. *Current Practice of Clinical Electroencephalography*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.

Kimura J. *Electrodiagnosis in Diseases of Nerve and Muscle*. 3rd ed. New York, NY: Oxford University Press; 2001.

Kimura J, Kohara N. Electrodiagnosis of neuromuscular disorders. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, eds. *Neurology in Clinical Practice*. 3rd ed. Boston, MA: Butterworth-Heineman; 2000:497–519.

Kuntz KM, Kokmen E, Stevens JC, Miller P, Offord KP, Ho MM. Post-lumbar puncture headaches: experience in 501 consecutive procedures. *Neurology*. 1992;42:1884–1887.

Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292–302.

Preston DC, Shapiro BE. *Electromyography and Neuromuscular Disorders*. 2nd ed. Philadelphia, PA: Elsevier; 2005.

Niedermeyer E, Lopes da Silva F. *Electroencephalography—Basic Principles, Clinical Applications, and Related Fields*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

Whiteley W, Al-Shahi R, Warlow CP, et al. CSF opening pressure: reference interval and the effect of body mass index. *Neurology*. 2006;67:1690–1691.

CHAPTER

34 Approach to Common Office Problems of Pediatric Neurology

Eugene R. Schnitzler

Currently the majority of pediatric neurologic consultations are provided in an outpatient clinic or office-based setting. The neurologist who sees children and adolescents may either be a formally trained pediatric neurologist or an adult neurologist with experience and interest in child neurology. In either case, it is important that the physician be able to develop and maintain a rapport with children and their parents. The physician and office staff should provide a gentle and friendly environment for pediatric patients including a waiting area with developmentally appropriate toys and reading materials. It is important that the office be punctual about appointments, and waiting times should be minimized.

Most childhood neurologic disorders are chronic, resulting in the opportunity to form long-term trusting physician–patient/parent relationships. The success of these relationships often hinges on the neurologist's ability to demonstrate empathy, optimism, and encouragement despite the realities of the patient's condition. Finally, pediatric neurologic consultation requires a harmonious working relationship with the child's pediatrician or family practice physician. The primary care physician is usually the first provider to screen for neurologic and developmental disorders. It is crucial to promptly inform the primary care provider regarding the outcome of the child's consultation and the resultant diagnostic and treatment recommendations.

Many neurologic conditions seen in children are also encountered in adults. Refer to the appropriate chapters in this book for further review of these topics. This chapter will focus on the more common diagnoses seen in office pediatric neurology. The current national shortage of pediatric neurologists suggests that adult neurologists should familiarize themselves with these disorders and become more accustomed to working with children.

I. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

A. Introduction. Attention-deficit/hyperactivity disorder (ADHD) is usually diagnosed in elementary school age children. The incidence is estimated at 10% with boys being affected twice as often as girls. The pathophysiology is thought to be secondary to decreased concentrations of dopamine in the striatum. The presenting complaints are hyperactivity, impulsivity, distractibility, inattentiveness, and poor concentration. Typically, the school will express concerns to the parents and suggest pediatric, psychiatric, or neurologic consultation. The parent may initially be in a state of denial or resistance to the diagnosis. There are three recognized ADHD subtypes:

1. **ADHD—predominately hyperactive–impulsive type**
2. **ADHD—predominately inattentive type**
3. **ADHD—combined type**

Although boys usually present with hyperactive–impulsive or combined type ADHD, it is common for girls to present with the inattentive type. Inattentiveness can be manifested by prolonged staring spells because of daydreaming, which may be confused with absence epilepsy by the naïve observer. Hyperactivity and impulsivity are characterized by excessive motoric behavior, fidgeting, and inability to stay seated. The child refuses to take turns, blurts out answers, and interrupts or disrupts the classroom. Organizational skills are particularly lacking and the child often fails to turn in homework assignments. ADHD may also be accompanied by comorbid conditions such as anxiety, depression, oppositional defiant disorder, obsessive compulsive disorder, learning disabilities, tics, and Tourette's syndrome. Some of these disorders are discussed further in Chapter 28.

B. Evaluation. The history should focus on the child's development and behavioral patterns. Family history of ADHD symptoms in a parent or sibling is very common. Developmental delays in speech and language should raise concern about autism pervasive developmental disorder (PDD), or mental retardation. Inquiries should be particularly directed to structural heart problems or arrhythmias, which may be a contraindication to pharmacologic management.

Most children with ADHD have normal neurologic examinations. Some may have neurologic soft signs such as mirror movements. However, the child with ADHD hyperactive–impulsive type is easily diagnosed by direct observation of excessive motoric and impulsive behavior in the office. The parent may be embarrassed or oblivious to the situation and unable to control the child. On the other hand, the child with ADHD inattentive type may be perfectly behaved and asymptomatic in the office setting.

It is imperative to auscultate the heart and check resting pulse and blood pressure. If a heart murmur or arrhythmia is detected, consideration should be given to obtaining an EKG and cardiology consultation prior to initiating medications. A history of tics or observation of tics on examination suggests a transient tic disorder or Tourette's syndrome. Imaging studies are not routinely indicated despite some reports of abnormalities on positron emission tomography scans. EEG is also not routinely required but may be necessary to differentiate inattentive staring from absence seizures. Children with dysmorphic features may warrant chromosome analysis. Screening for thyroid diseases, anemia, or lead toxicity may be indicated in selected cases. Diagnosis is enhanced by psychological testing including standardized behavioral questionnaires and continuous performance testing by computer.

Although once thought to be exclusive to childhood, ADHD is now recognized as an entity in adolescents and adults. The diagnosis is not "outgrown," although the more visible features of hyperactivity and impulsivity may be less obvious after puberty. It is not uncommon for parents of children diagnosed with ADHD to recognize similar symptoms in themselves and to seek out medical advice.

Children with ADHD should be managed with the so-called multimodal treatment including an individual education plan or 504 plan provided by the local school district. In addition, parent training in behavioral management and counseling for the child and family may be beneficial. Stimulant medications are also an essential component for successful management of ADHD and have been shown to improve long-term outcomes. These are primarily methylphenidate and amphetamine salt combinations. Both are available in extended release formulations that reduce the need for medication administration in school. Nonstimulant medications including atomoxetine, clonidine, and guanfacine are other options.

II. DEVELOPMENTAL DELAY

Developmental delay is defined as the failure to achieve an anticipated milestone at the age-appropriate time. Delays can occur in a distinct area such as gross motor, fine motor, language, or cognitive skills. When more than one area of development is affected, the term *global developmental delay* (GDD) is used. GDD is seen commonly by developmental pediatricians and pediatric neurologists and is estimated to affect 5% to 10% of the pediatric population.

A. Static encephalopathy. Infants and toddlers with static encephalopathy fail to achieve motor and/or speech and language milestones on time. The milestone may subsequently be attained, but at a later than expected time or with abnormalities. Once the milestone is achieved, it is generally not lost.

Static encephalopathies can be caused by numerous conditions. These include chromosomal and genetic disorders, cerebral malformations, intrauterine infections, meningitis, encephalitis, trauma, intraventricular hemorrhage, and hypoxic–ischemic encephalopathy. Nevertheless, a substantial percentage of static encephalopathies are idiopathic with regard to etiology. Although most cases of static encephalopathy will result in GDD, milder or more localized cases may result in distinct neurologic or

developmental disorders. Examples include cerebral palsy (CP) and autistic spectrum disorders (ASDs).

B. Cerebral palsy. Static encephalopathies that primarily affect motor control areas of the brain are described by the term *cp*. CP occurs with a prevalence of 2.5 per 1,000 live births. A higher prevalence may be seen in premature and low-birth weight infants. It is further classified based on severity and distribution of spasticity. The most severe variant, spastic quadriplegia, results in spasticity in all four extremities. There is marked delay in motor milestones, accompanied by increased tone, brisk deep tendon reflexes (DTRs), and positive Babinski signs. Seizures, microcephaly, feeding difficulties, and psychomotor retardation are common features. Milder variants of CP such as spastic diplegia are common in premature infants following intraventricular hemorrhage and periventricular leukomalacia. Infants with spastic diplegia show spasticity and weakness primarily in the lower extremities with relative sparing of the arms. Infants with hemiplegic CP present with unilateral weakness and spasticity. Intrauterine arterial infarctions, periventricular hemorrhages, and cerebral malformations are the most common etiologies.

C. Autistic spectrum disorders (ASD). Autism and developmental language disorders may be considered as static encephalopathies that primarily affect speech and language development. Autism is sometimes grouped under the broader heading of PDD. Asperger's syndrome is considered to be a form of high functioning autism. Children with autism demonstrate a wide range of deficits in socialization and language. Hence, the term ASD is now used to describe these children.

Symptoms of autism usually begin in the second year of life. Parents often report that early motor milestones developed normally. However, there is marked delay in the acquisition of speech and language. Echolalia is frequently present with the child simply repeating or parroting phrases. It is typical for the child not to respond to his or her name and to appear socially withdrawn or aloof. Stereotypic behaviors, such as spinning, rocking, or hand flapping, are commonly observed. Children and adults with Asperger's syndrome may have normal speech and cognition but lack age appropriate understanding of language nuances and socialization skills. They tend to be loners with a narrow range of interests, mechanical speech patterns, and stereotypic behaviors. The incidence of ASD appears to be rising and is currently estimated at 1 in 110 live births. However, it is speculated that this increased incidence may in part be because of enhanced public awareness and inclusion of children with Asperger's syndrome.

The etiology of autism is unknown but appears to be multifactorial. In the past two decades, several alternative hypotheses including measles immunization, thiomersal toxicity, and gluten-casein sensitivity have been promulgated and subsequently refuted. Genetic predisposition clearly plays an important role as indicated by concordance in twins and siblings. Autism has been linked to tuberous sclerosis, fragile X syndrome, Rett's syndrome, and Angelman's syndrome. In addition, numerous suspicious genetic duplications and deletions as well as copy-number variations are being identified by chromosome microarray analysis.

D. Progressive cognitive impairment. In progressive cognitive impairment, acquisition of milestones initially decelerates. Subsequently, there is a loss of previously achieved skills. There may be a combined loss of motor, coordination, and sensory and cognitive functions. Alternatively, loss of skills and functions in one area may precede losses in other areas. The pattern and sequence of regression may yield clues to the diagnosis.

E. Disorders of white matter (leukodystrophies) initially present with loss of motor milestones and increasing spasticity. There may also be a loss of vision. MRI scans demonstrate white matter demyelination. Peripheral neuropathy is often a characteristic feature as well. This can be demonstrated by slowing of peripheral nerve conduction velocities. Visual and auditory evoked response studies may also demonstrate slowing. Some examples of leukodystrophies include globoid cell leukodystrophy, metachromatic leukodystrophy, Alexander's disease, Canavan's disease, Pelizaeus–Merzbacher's disease, and adrenoleukodystrophy. Age of onset, patterns of loss of function, genetic testing, and MRI findings can help to distinguish the various leukodystrophies.

F. Disorders of gray matter often present with seizures and loss of cognitive skills. These include amino and organic acidurias, Tay–Sachs' disease, ceroid lipofuscinosis, Rett's syndrome, and AIDS encephalopathy.

G. Disorders with prominent movement disorder include Wilson's disease (hepatolenticular degeneration), pantothenate kinase associated neurodegeneration, and Niemann–Pick's disease. These may present with dysarthria, dysphagia, dystonia, chorea, and spasticity. Juvenile Huntington's disease and Parkinson's disease may present with chorea, rigidity, and tremor. Ataxia is a prominent feature of ataxia telangiectasia, Refsum's disease, abetalipoproteinemia, and Friedreich's ataxia.

H. Neurocutaneous disorders. These genetic conditions are characterized by skin lesions and CNS findings. Developmental delays are observed as well. Neurofibromatosis type 1 (Von Recklinghausen's disease) has an autosomal dominant pattern of transmission and has been localized to chromosome 17. Spontaneous mutations are also common. The condition is characterized by multiple café au lait spots, often with axillary freckling and neurofibromas on the skin. Increased head circumference is associated as are Lisch nodules in the iris, scoliosis, pseudoarthosis, and hypertension. There is a higher incidence of optic gliomas and other CNS tumors, so that periodic neuroimaging of the brain and orbits is recommended. Neurofibromatosis type 2 is less common and is characterized by café au lait spots and vestibular schwannomas. Tuberous sclerosis complex has several characteristic skin lesions including scattered hypopigmented macules, shagreen patches, adenoma sebaceum, and subungual fibromas. Subependymal nodules and giant cell astrocytomas are seen in the brain. Cardiac rhabdomyomas and renal angiomyolipomas also occur. Affected children are at risk for infantile spasms, partial seizures, ASDs, and GDDs.

Sturge–Weber syndrome presents with port wine birthmarks in the trigeminal nerve distribution and ipsilateral brain hemangiomas. Affected children also have contralateral focal motor seizures and hemiparesis. Other rare neurocutaneous syndromes associated with developmental delays and epilepsy are incontinentia pigmenti and hypomelanosis of Ito.

I. Evaluation. Children referred for specialty evaluation of developmental delay should have already been screened by their pediatricians. The American Academy of Pediatrics recommends such screening utilizing a standardized test at the 9 month, 18 month, and 24 or 30 month well-child care visits. In the absence of such screening, the neurologist should consider administering a standardized general developmental screening test as a preliminary assessment. Examples of validated developmental screening tests include the Ages and Stages Questionnaires, Child Development Inventory, and the Bayley Infant Neurodevelopmental Screen. When screening for autism or Asperger's syndrome, more specific inventories such as the Childhood Autism Rating Scale, Modified Checklist for Autism in Toddlers, and the Asperger Syndrome Diagnostic Scale should be utilized.

A thorough history should be obtained with particular attention to gestational age, pregnancy, labor, and delivery. Hospitalizations in the NICU at birth should be reviewed for high-risk neurologic problems including neonatal seizures, intraventricular hemorrhages, meningitis, and hydrocephalus. Family history should be reviewed for close relatives with similar delays or diagnosed causes of developmental delay. Developmental milestones should be tabulated to assess for patterns of static or progressive encephalopathies.

A complete examination should be done with particular attention to the nervous system. It is especially important to observe and record somatic growth, head circumference, dysmorphic features, birthmarks, and developmental milestones. Audiologic assessment should routinely be obtained in cases of speech and language delays. Referral to a pediatric ophthalmologist is particularly relevant if lack of eye contact, impaired visual tracking, strabismus, and corneal opacities are noted. Most states now routinely screen newborn infants for hypothyroidism and several of the treatable metabolic disorders. However, these should be repeated if warranted by the patient's presenting signs and symptoms. Screening for lead exposure should be considered if environmental risk factors are identified.

If there is a positive family history of developmental delays or if autism is suspected, genetic testing is indicated. Autistic children should be routinely screened for fragile X syndrome. In addition, chromosome microarray analysis should be obtained with particular attention to duplication at the 15q11–q13 and deletion of 22q11.2 regions. If Rett's syndrome is a consideration, screening for MeCP2 is recommended.

EEG and MRI are not routinely indicated in cases of static encephalopathies. However, an EEG should be obtained in patients with suspicion of seizures. An EEG should also be considered in patients with regression of language skills to rule out epileptogenic encephalopathies such as Landau–Kleffner syndrome.

CT and MRI require sedation and are reserved for patients with abnormalities of head circumference, particularly progressive macrocephaly or microcephaly. Focal or lateralizing neurologic signs (e.g., hemiparesis) are also an indication for imaging studies. Progressive encephalopathies also warrant an MRI to assess for degenerative or structural abnormalities. Periodic neuroimaging is indicated to monitor the progress of children with neurocutaneous syndromes.

III. MOTOR DISORDERS

Normal motor development follows a defined sequence of milestones. By 2 months of age, the infant lifts the head from prone. Rolling over and transferring objects is accomplished by 5 to 6 months. Sitting independently occurs by 8 to 9 months and walking independently between 12 and 15 months. Delays in the acquisition of milestones are seen in children with hypotonia and weakness. This condition is also described as floppy infant syndrome.

A. Central or cerebral hypotonia. Hypotonia may be the initial manifestation of CP. These infants may have a history of hypoxic–ischemic encephalopathy, intraventricular hemorrhage, and/or neonatal seizures. Cerebral dysgenesis should be suspected if there are dysmorphic features or other congenital malformations. Although these infants are initially hypotonic, over time muscle tone increases accompanied by spasticity, weakness, hyperreflexia, and positive Babinski signs.

Children with chromosome abnormalities and genetic syndromes are also typically hypotonic. Examples include Down's syndrome, Lowe's syndrome (oculocerebrorenal syndrome), familial dysautonomia (Riley–Day syndrome), and Prader–Willi syndrome. Prader–Willi syndrome is further characterized by poor feeding in the neonatal period and hypogonadism.

Benign congenital hypotonia may be a mild variant of cerebral hypotonia. Infants with benign congenital hypotonia are hypotonic in infancy but gradually recover muscle tone and motor milestones. However, mild developmental delays and learning problems may later be noted in such children.

B. Spinal cord injuries. Stretching of the cord may result from traction during delivery, particularly with breech presentation. The infant is often comatose and flaccid at birth and may not survive. Milder cervical cord injuries present with residual hypotonia and must be distinguished from cerebral and lower-motor unit disorders.

C. Lower-motor unit disorders.

1. **Anterior horn cell disorders.** Spinal muscular atrophy (SMA) is caused by degeneration of anterior horn cells in the spinal cord and brainstem. SMA type 1 (Werdnig–Hoffman disease) results in severe hypotonia weakness, absent muscle stretch reflexes, and tongue fasciculations. Affected children usually die from respiratory complications by 1 year of age. Milder variants (SMA types 2 and 3) present later in infancy or childhood. Affected children survive longer, but also have weakness, hypotonia, areflexia, muscle fasciculations, and arthrogryposis.
2. **Neuropathies.** Hereditary neuropathies generally present beyond infancy. They are divided into hereditary motor sensory neuropathy (HMSN), hereditary motor, and hereditary sensory and autonomic subtypes. Charcot–Marie–Tooth, the most common HMSN, presents in childhood with peroneal muscle atrophy foot-drop, pes cavus, and absent DTRs. Neuropathy may also be a manifestation of systemic diseases such as diabetes and autoimmune disorders as well as leukodystrophies and hereditary ataxia. A number of medications including vincristine, isoniazid, phenytoin, and pyridoxine can cause neuropathy.
3. **Neuromuscular junction disorders.** Transient neonatal myasthenia syndrome may be seen in infants born to mothers with myasthenia gravis. Feeding problems, weak cry, facial weakness, and hypotonia are common features. Genetic myasthenia syndromes

are rarer and are characterized by respiratory difficulties, poor feeding, weakness, ptosis, and ophthalmoplegia. Infantile botulism mimics myasthenia, but affected infants also show pupil dilatation and constipation.

4. **Myopathy.** Congenital myopathies present in infancy with hypotonia, motor delays, and proximal muscle weakness. Numerous variants have been described, each with unique findings on muscle biopsy. These include nemaline myopathy, myotubular myopathy, congenital fiber-type disproportion, and central core disease. Metabolic myopathies include lysosomal enzyme deficiencies such as Pompe's disease (acid maltase deficiency). This disorder presents in infancy with weakness, hypotonia, and cardiomyopathy resulting in heart failure. Rare mitochondrial myopathies can also be accompanied by hypotonia and lactic acidosis. Congenital muscular dystrophy presents with hypotonia and arthrogryposis at birth and may also show CNS involvement. Congenital myotonic dystrophy occurs in infants of mothers with the disease. Hypotonia, facial diplegia, arthrogryposis, and gastroparesis are the common presenting signs. Childhood onset muscular dystrophy is reviewed in Chapter 47.

D. Evaluation. Neurologic and general examination helps to distinguish central hypotonia from lower-motor unit disorders. Muscle stretch reflexes are present and may be brisk in central hypotonia but are absent or diminished in lower-motor unit disorders. Tongue fasciculations are seen in SMA. Congenital malformations, dysmorphic features, and abnormalities of head size and shape suggest cerebral dysgenesis. Arthrogryposis suggests an SMA or CMD variant.

Neuroimaging is indicated if cerebral dysgenesis is suspected. Workup for lower-motor unit disorders includes measurement of creatine kinase level, EMG, nerve conduction velocity, and muscle biopsy. The edrophonium chloride test can confirm myasthenia gravis. There are now specific DNA probes available for the SMA subtypes, myotonic dystrophy congenital muscular dystrophy, and Prader–Willi's syndrome.

IV. ATAXIA

A. Definition. Ataxia refers to lack of coordination and impaired control of voluntary movements and balance. The cerebellum controls these functions in conjunction with the sensory input from the vestibular system, basal ganglia, and spinal cord.

B. Acute ataxia. Intoxication, particularly from alcohol, sedatives, antihistamines, and anticonvulsants may cause ataxia. Acute postviral cerebellar ataxia usually occurs in preschool children. The onset often coincides with the end of a viral illness, particularly varicella. The onset is very dramatic with the child suddenly becoming unable to walk. Nystagmus may also occur. Recovery is usually complete but may take up to several months. Viral encephalitis with cerebellar and/or brainstem involvement can also present with acute ataxia. There may be accompanying cranial nerve deficits. Guillain–Barré syndrome (GBS; Fisher variant of GBS) may present with similar findings. Kinsbourne syndrome consists of acute ataxia accompanied by opsoclonus and myoclonus. It is thought to be a paraneoplastic condition secondary to occult neuroblastoma.

C. Chronic progressive ataxia. Posterior fossa tumors are the most common brain tumors in childhood. Medulloblastoma, ependymoma, cerebellar astrocytoma, and brainstem glioma can all present with slowly progressive ataxia. The most common recessive genetic disorder presenting with childhood onset progressive ataxia is Friedreich's ataxia. In addition to ataxia, patients develop scoliosis, cardiomyopathy, retinitis pigmentosa, cataracts, and hearing loss. Absent DTRs and positive Babinski signs are typically noted. Friedreich's ataxia has been localized to an unstable GAA triplet repeat of the frataxin gene on chromosome 9q13. Other rare degenerative and metabolic causes of chronic progressive ataxia include ataxia telangiectasia, abetalipoproteinemia, Refsum's disease, vitamin E deficiency, biotinidase deficiency, and a multiple carboxylase deficiency. In addition more than 20 variants of autosomal dominant spinocerebellar atrophy have been described with ages of onset ranging from childhood to late adulthood.

D. Chronic non-progressive ataxia. This is typically associated with malformations of the cerebellum and posterior fossa such as Dandy–Walker's syndrome, Chiari's malformation, and Joubert's syndrome.

E. Intermittent ataxia. This may accompany concussion and may also be seen as an ictal or postictal feature of epilepsy. Basilar migraine often presents with ataxia and vertigo followed by occipital headache. Benign paroxysmal vertigo presents in early childhood with sudden brief episodes of pallor, nystagmus, and inability to walk. Ataxia presenting acutely or intermittently may also be a feature of childhood onset multiple sclerosis.

Rare genetic causes of episodic ataxia include urea cycle disorders, intermittent maple syrup urine disease, and Hartnup's disease. Episodic ataxia type 1 is caused by a dominantly inherited mutation of the voltage-gated K^+ channel gene (KCNA1) located at chromosome 12p13. Affected patients present with brief episodes of ataxia sometimes provoked by startle. Myokymia and large calves are associated features. Episodic ataxia type 2 has been linked to a calcium channel gene (CACNA1A) at chromosome 19p13. Attacks of ataxia begin in childhood. Some are prolonged and resemble basal artery migraine.

F. Evaluation. Because ataxia may be congenital, acute, chronic progressive, chronic non-progressive, or intermittent, it is important to establish the duration and pattern. Inquiry should be made regarding possible antecedent trauma, toxin exposure, medications, infections, and seizure disorder. Developmental delays and/or regression may also accompany ataxia due to many of these disorders.

G. Examination. Truncal ataxia is assessed by checking gait, station, tandem gait and Romberg's sign. Limb ataxia is tested by evaluating finger to nose, heel-to-shin, and rapid alternating movements. Ability to perform tests of coordination is age-dependent and also requires the cognitive understanding of the child. In preverbal children, assessment of gait and coordination is done by observation of the child's movements and activities.

H. Diagnostic studies. Neuroimaging (CT or MRI) is required for most acute ataxias unless intoxication or acute postviral ataxia is determined to be the cause. For acute ataxias, obtain toxicology screening, particularly for alcohol and anticonvulsant drugs, and urine catecholamines. Chronic ataxias also require neuroimaging as well as selective laboratory studies such as urine amino acids, ammonia, phytanic acid, biotin, cholesterol, and cholestanol levels. For the intermittent ataxias, consider selective testing as appropriate for metabolic and genetic disorders.

V. HEADACHE

A. Acute headache. Headache is a common feature of systemic febrile illnesses and viral syndromes in children. Bacterial illnesses such as otitis media, sinusitis, and meningitis are also accompanied by headaches. Sinusitis may result in facial, frontal, or retro-orbital pain. The pain of otitis media may localize to the temporal region. Meningitis may manifest with diffuse headache, fever, nuchal rigidity, altered mental status, and seizures.

The child who presents with acute headache and is afebrile may still have an infectious illness. However, it is more likely that the etiology is the first tension or migraine headache. Head injuries with subarachnoid, subdural, or epidural hemorrhage must be ruled out. Concussions are also typically followed by acute and sometimes chronic headaches. Idiopathic intracranial hypertension (pseudotumor cerebri), hypertension, and medication side effects are also considerations.

B. Chronic headache.

1. **Migraine** is common in childhood affecting up to 5% of preadolescent children and 10% of teenagers. The gender ratio is even in children but females predominate in puberty and adolescence. Family history in a first-degree relative is very common and helps to make the diagnosis. Migraine may appear in early childhood. In such cases, migraine equivalents such as cyclic vomiting, benign paroxysmal torticollis, and benign

paroxysmal vertigo are the more likely manifestations. Ophthalmoplegic migraine has also been reported in infancy.

In children, common migraines are much more typical than the classical type. The child complains of a moderate to severe diffuse or bifrontal headache accompanied by nausea, vomiting, pallor, and irritability. Older children may be able to better localize the headaches and will describe a throbbing or pulsating quality. The headache may occur at random times and may on occasion awaken the child from sleep. Migraines in children are typically relieved within a few hours by sleep in a darkened room and minor analgesics. Caffeine withdrawal, nitrates, chocolate, monosodium glutamate, alcohol, dairy products, and numerous other foods are thought to trigger migraines. Environmental factors such as secondhand smoke, automobile emissions, perfumes, and atmospheric pressure changes have also been implicated.

Complicated migraines are also seen in childhood and may require further investigations including neuroimaging. Ophthalmoplegic migraine presents with headache and irritability, followed by unilateral third nerve palsy. This is manifested by ptosis, mydriasis, and eversion of the affected eye, which may last hours to days. Basilar migraine presents with posterior headache, nausea, vomiting, ataxia, vertigo, and on occasion, loss of consciousness. Hemiplegic migraine may mimic stroke with unilateral hemisensory, hemiparetic, and aphasic symptoms followed by a severe contralateral headache.

2. **Tension headache.** These headaches occur in children as well as adults. The headaches are frontal or occipital or may have a "hatband" distribution. They tend to occur in the afternoon or evening and have been associated with stress or anxiety. When these headaches occur on a daily basis, school avoidance should be suspected. Chronic daily headache is typically seen in adolescent girls and is defined by more than 15 headaches per month. This condition is also sometimes described as "chronic migraine." Sleep deprivation, skipping meals, excessive gum chewing, smoking, and caffeine withdrawal may exacerbate the headaches. Overuse of analgesics can complicate the situation and result in so-called "rebound" headaches. Biofeedback and/or psychological counseling may be required to treat underlying comorbid conditions such as anxiety, depression, ADHD, and conduct disorders.

Chronic daily headaches caused by mass lesions are associated with increasing intracranial pressure. Abnormalities on neurologic examination appear in the great majority of such children within 4 months of the onset of headaches. These may include papilledema, cranial nerve abnormalities, ataxia, dysmetria, hemiparesis, or focal sensory signs. Reflex asymmetries and a unilateral Babinski's sign may also be present.

Idiopathic intracranial hypertension (pseudotumor cerebri) presents with acute or chronic headaches, vomiting, and double vision accompanied by papilledema. It is commonly seen in obese adolescent girls. A sixth nerve paresis may also be noted. Lumbar puncture (LP) reveals elevated CSF pressure and may partially relieve the condition. The mechanism of action is unknown, but pseudotumor cerebri has been associated with use of steroids, vitamin A, and tetracyclines. Cerebral venous thrombosis and mastoiditis have also been linked to the condition.

C. **Evaluation.** It is important to assess the frequency, severity, location, and time of day of the headaches. Severity can be assessed by asking the child or parent to grade the headache from 1 to 10. The history should include inquiry regarding development, head injuries, seizures, learning or attention problems, and family members with recurrent headaches. Information should be requested regarding lifestyle factors including caffeine consumption, sleep habits, meal patterns, excessive gum chewing, and exposure to secondhand smoke. In girls, the onset of menarche should be noted because it may be heralded by migraine headaches.

Blood pressure and pulse should be checked personally by the physician or a reliable assistant. A complete general and neurologic examination is required for every child who presents with headaches. The head circumference should be measured. The skull and neck should be ausculated for bruits. The eyes, ears, nose, and throat should be examined including palpation for cervical nodes and sinus tenderness. The temporomandibular joint should be palpated and ausculated for misalignments and clicks. The teeth should be checked for caries, malocclusions, and newly installed braces or appliances.

Most children with headaches do not require neuroimaging provided rapport is established with the parents and timely follow-up can be arranged. If the history and examination suggests acute CNS infection or idiopathic intracranial hypertension, an LP should be considered. Acute hypertension may require hospitalization and workup for renal or cardiac diseases. If acute head injury or concussion is suspected, an emergency noncontract CT scan should be obtained to check for intracranial hemorrhage. Chronic recurrent headaches with typical migrainous or tension features do not require imaging unless they remain refractory to treatment. An MRI should be obtained in children with complicated migraine and idiopathic intracranial hypertension or if abnormalities are present on neurologic examination. On occasion, an anxious parent may insist on neuroimaging for the child despite the reassurance that such a procedure is unnecessary. In such instances, it is usually prudent to acquiesce to the parent's request provided there is no obvious contraindication to the neuroimaging procedure.

The reader is referred to Chapters 20 and 21 for further information on the approach to patients with acute and chronic headaches.

VI. NONEPILEPTIC PAROXYSMAL DISORDERS

Nonepileptic paroxysmal disorders are defined by their intermittent, recurrent, and abrupt presentation. Between episodes the patient feels well and has no complaints. It is particularly important to distinguish these episodic conditions from epilepsy. Childhood epilepsies are discussed in detail in Chapter 38.

A. Evaluation. A detailed description of the event by a reliable observer is essential for proper classification and diagnosis. Older children can also contribute their personal recollections. Inquiry should be particularly directed toward triggering events or precipitating factors. A videotape of the episode may be particularly useful. Examination is normal in most cases. Diagnostic studies are generally not required. On occasion EEG and video EEG may be necessary to rule out epilepsy.

B. Breath-holding spells. These are benign, but frightening, paroxysmal episodes that may result in a brief loss of consciousness. Cyanotic syncope occurs in infants and children between 6 months and 4 years of age. The family history is often positive. The child first cries because of anxiety, frustration, or pain. Following prolonged expiration, breathing ceases and the child becomes cyanotic, hypotonic, and briefly unresponsive. Recovery usually occurs quickly but on occasion some brief tonic–clonic movements followed by sleep may occur.

Another variant of breath-holding is pallid syncope. This is usually initiated by a minor head injury, which is thought to trigger a brief reflex asystole. The child becomes pale, limp, and is briefly unconscious.

Breath-holding spells can be diagnosed clinically by the stereotypic sequence of events preceding each episode. On rare occasions or to lessen parental anxiety, an EEG can be done to distinguish these episodes from epileptic seizures.

C. Syncope (fainting). Syncope is common in children, especially during adolescence. It is induced by a transient decrease in blood flow to the brain secondary to a vasovagal reflex. It is almost always precipitated by triggering stimuli such as change of position, pain, or extreme fear or anxiety.

The syncopal event may be preceded by an "aura" of blurry vision, dizziness, and/or tinnitus. The child then becomes pale and clammy and loses consciousness with an accompanying fall. Brief stiffening, upward eye rolling, vocalizations, and tremulous movements are not uncommon. Tongue biting is unusual in syncope. Recovery of consciousness usually occurs within a minute. In most instances, syncope is considered to be a common benign occurrence that does not warrant extensive neurodiagnostic testing. If syncope is prolonged or recurrent, a cardiology referral with ECG monitoring may be necessary. Syncope is reviewed in more detail in Chapter 7.

D. Other. Episodic weakness, ataxia, tremor, chorea, vertigo, and sensory disturbances are reviewed elsewhere in this chapter or in other chapters under the appropriate

headings. However, several other paroxysmal neurologic disorders are unique to infants and young children.

1. **Spasmus nutans** begins in infancy and resolves spontaneously in early childhood. It consists of three cardinal features: head bobbing, torticollis, and nystagmus. Diagnosis may warrant neuroimaging of the brain and orbits to rule out neoplasms, which can rarely present with similar signs.
2. **Sandifer's syndrome** is seen in infancy and consists of paroxysmal opisthotonic posturing sometimes accompanied by vomiting and apnea. The underlying etiology is gastroesophageal reflux, which requires pediatric gastrointestinal consultation.
3. **Paroxysmal infant shuddering** or shivering occurs during wakefulness and may raise concerns about seizures. The child appears to momentarily shiver as if having a chill. Such episodes often occur frequently enough to be captured on videotape in which case they are easily distinguishable from clinical seizures. Later in life, essential tremor may be associated with a history of infant shuddering.
4. **Masturbation** is occasionally seen in infants and young children and may be confused with seizures. These episodes consist of prolonged rocking movements of the pelvis and thighs. Altered breathing, flushing, sweating, and staring are typically seen. These episodes resolve over time with parental reassurance.

VII. ABNORMALITIES OF HEAD SIZE

A. Normocephaly is defined as a head circumference measurement between the 2nd and 98th percentile. A head circumference > 98th percentile is macrocephaly, and a head circumference < 2nd percentile is microcephaly. Normally the head should grow on a specific percentile. Deviation of growth from the expected percentile should prompt further evaluation and investigations. Macrocephaly and microcephaly are both associated with higher incidences of CNS pathology and developmental delays.

B. Macrocephaly may be familial, in which case at least one parent's head will also be large. Differential diagnosis also includes hydrocephalus, which may be communicating or obstructive. Rare metabolic disorders including galactosemia, maple syrup urine disease, mucopolysaccharidoses, and Canavan's disease are associated with macrocephaly. Children with genetic conditions including achondroplasia, fragile X syndrome, cerebral gigantism (Sotos' syndrome), and the neurocutaneous disorders commonly have large heads. Benign subdural collections present with progressive enlargement of head circumference, but without signs of increased intracranial pressure.

C. Microcephaly may be because of genetic causes or cerebral dysgenesis and is commonly associated with congenital syndromes. It is also frequently seen following hypoxic–ischemic encephalopathy, intrauterine infections, and postnatal infection. Craniosynostosis can cause progressive microcephaly when more than one suture is affected. Rett's syndrome also presents with progressive microcephaly.

D. Evaluation. The history may reveal developmental delay or regression. Symptoms of increased intracranial pressure include emesis, irritability, and somnolence. Examination may reveal signs of increased intracranial pressure including bulging fontanelle, sunsetting of the eyes, papilledema, or a sixth nerve palsy. The head circumference should be plotted on a standardized growth chart and serial measurements should be obtained. Neuroimaging is indicated in most cases of abnormal head size. Exceptions include familial macrocephaly and possibly benign subdural collections. Chromosomes and metabolic studies are also considerations if cerebral dysgenesis or storage diseases are suspected.

Recommended Readings

Council on Children with Developmental Disabilities, et al. (American Academy of Pediatrics Policy Statement) Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. *Pediatrics.* 2006;118:405–420.

DiMario, FJ. *Non-Epileptic Childhood Paroxysmal Disorders*. New York, NY: Oxford; 2009.
Espay AJ, Biller J. *Concise Neurology*. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2011.
Fenichel GM. *Clinical Pediatric Neurology: A Signs and Symptoms Approach*. 5th ed. Philadelphia, PA: Elsevier Saunders; 2005.
Klein O, Pierre-Kahn A, Boddaert N, et al. Dandy-Walker malformation: prenatal diagnosis and prognosis. *Childs Nerv Syst*. 2003;19:484–489.
Lewis M. *Child and Adolescent Psychiatry: A Comprehensive Textbook*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002.
Maria BL. *Current Management in Child Neurology*. 3rd ed. Hamilton, ON: BC Decker, Inc.; 2005.
Parisi MA. Clinical and molecular features of Joubert syndrome and related disorders. *Am J Med Genet C Semin Med Genet.* 2009;15:326–340.
Reiff M. *ADHD: A Complete and Authoritative Guide*. Elk Grove Village, IL: American Academy of Pediatrics; 2004.
Robertson WC, Schnitzler ER. Ophthalmoplegic migraine in infancy. *Pediatrics.* 1978;61:886–888.
Silberstein SD, Lipton RB, Goadsby, PJ. *Headache in Clinical Practice*. 2nd ed. London, UK: Martin Dunitz; 2002.
Tervo RC. Identifying patterns of developmental delays can help diagnose neurodevelopmental disorders. *Clin Pediat (Phila).* 2006;45:509–517.
Wyllie E. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.

CHAPTER

35 Approach to Ethical Issues in Neurology

Michael P. McQuillen

Clinical ethics—the business of being human in the interchange between physician and patient—has been an integral part of that interchange for as long as there has been a profession of medicine. Until the past several decades, however, it was assumed that being a physician meant being ethical; that everyone's ethics were the same (or at least of equivalent worth); and that there was no underlying theory or set of standards necessary for ethical decision making. In part, this state of affairs was a reflection of the simplicity of life in general, and of medicine in particular. With advances in technology, more options became possible—options to evaluate new forms of treatment (clinical research) as well as to utilize proven diagnostic and therapeutic modalities (with their inherent risk-benefit calculus). In today's world, questions of *who* should make *which* decisions in *what* circumstances, as well as who could and should *pay* for the costs of implementing those decisions, are being asked. As these changes have taken place, particular judgments no longer stood in isolation, but rather led to the formulation of **rules** that could govern in similar situations; a recognition of the **principles** upon which such rules might be based; and the development of **theories** underlying the principles—much as an understanding of anatomy, biochemistry, pathophysiology, and other basic sciences made it possible to clarify approaches to the complicated problems of stroke (for example). Some theorists appealed directly to **conscience,** developed and refined in reflection on individual cases without the formality of the process just described. Underlying it all, however, was the realization that ethical problems arise in almost any clinical situation, and that such problems should be addressed just as systematically as any dimension of the given clinical situation. This realization called forth a new academic discipline (**biomedical** or **clinical ethics**) out of what previously had been purely philosophical and, in a sense, impractical thought (**theoretical** ethics). From this generic discipline, there has evolved a particular focus on neurologic ethical dilemmas (**neuroethics**).

In reality and from the start, the discipline of ethics found fertile ground in neurology, where ethical theory met real-life problems such as **brain death**; the **vegetative state**; and other conditions of incapacity, neurogenetic diseases, and a whole gamut of issues at the end of life. More recently, questions relating to neuroenhancement, stem cell research, and other matters have been added to the stew. Early on, this meeting generated encounters with the law and the recognition that what is ethical may not be legal, and *vice versa*. To plow the field, one must first understand the background of ethical theories; develop a structured approach to the recognition and solution of ethical problems; and understand how that approach helps to deal with particular problems, as well as developing an effective interface with the law.

I. ETHICAL THEORIES

Before accepting any ethical theory as a basis upon which practical judgments can be made, ultimately and validly, one should inquire whether the basis of theory is adequate to the task by virtue of its satisfying certain criteria, and then look to the basis of the theory to determine its usefulness and applicability. No one theory satisfies every clinical situation. Some are better adapted to one circumstance and others to another, while yet additional circumstances demand a hybrid of complementing theories.

A. Criteria of an adequate theory. Beauchamp and Childress set forth a series of questions that should be answered in the affirmative with regard to any particular theory

if that theory is to be regarded as adequate and helpful in a given clinical situation. Their questions are as follows:

1. **Is it clear?** Or is the language by which the theory is formulated so complex as to muddle the situation?
2. **Is it coherent?** Coherence is a necessary (although not sufficient) criterion of an adequate theory. It is missing when theory elements are in contradiction, one with another.
3. **Is it complete, or at least comprehensive?** Does the theory deal with all of the major questions raised in diverse clinical circumstances, or are there serious concerns on which the theory is silent?
4. **Is it simple?** Are there enough norms so that the theory can be used without confusion by clinicians, or are there so many that the answer becomes lost in practice?
5. **Can it explain and justify the conclusions reached with its help?** Or does it simply set forth in other words a preexistent, intuitive belief?
6. **Does it yield new insights?** Or does it only serve to repeat old convictions?
7. **Is it practical?** In short, does it provide a useful answer to the clinical problem or one that is attractive in theory only?

B. Types of ethical theory.

1. **Utilitarianism.** This theory looks to the *consequences* of acts and holds that an action is good if it produces more benefit than harm. It is the basis of the *risk–benefit analysis*, regularly used by clinicians in deciding and discussing with patients a recommended course of action in a given clinical circumstance. Problems arise when one looks for definitions of *risk* of harm and *benefit* (to or for whom?); to the relation between the individual acting or deciding and the society of which that individual is a member; and at single actions, each in isolation, or at classes of actions governed by rules that appeal to the principle of utility.
2. **Obligation-based theory.** The test of this theory is the **categorical imperative** of Immanuel Kant: The reason for an action should apply to everyone, and in all situations; moral rules are absolute. Problems arise when such rules—often abstract and legalistic, rather than relational—are found to be in conflict with each other in a particular circumstance.
3. **Virtue-based, or character, ethics.** This approach looks to the person acting and to the motives and desires that propel that person's actions. Because even the most virtuous person can act wrongly—even for the best of reasons—a viable ethical theory cannot rest on character alone.
4. **Rights-based ethics, or liberal individualism.** Rights are justified claims that an individual or group is entitled to make upon a society at large. Such claims, while protecting the interests of an individual, at the same time may impose a corresponding obligation upon others. Rights may be *positive* (requiring an action by others) or *negative* (precluding such action). Overemphasis on rights may neglect the legitimate demands of the society at large.
5. **Communitarian ethics.** Rather than the rights of the individual, communitarians look to the needs of society at large. Prescinding from *how* such needs may be articulated by *whom*, an overemphasis on this aspect of morality may neglect the legitimate interests of the individual.
6. **An ethics of care.** Sometimes referred to as *feminist* ethics, the focus of this approach is on a caring, attached relationship between persons and on the implications of such a relationship. Impartiality and balance may suffer as a consequence, the result being a less complete and practical system than obtains with other theories.
7. **Casuistry.** This term invokes an image of Jesuitical sophistry, but really refers to the need to make decisions according to the particulars of any given situation. In reality, it was St. Thomas Aquinas who first described "situation ethics," a much (and properly) maligned theory when reduced to the proposition that all morality is relative, dependent *solely* on the circumstances of an action. Every detail of the case is examined and weighed, and a judgment reached often by analogy to similar cases. The connection between cases provides a maxim to rule the case—but which maxim is given most credence in any particular situation, and why?
8. **Ethics based on principles, or "common morality."** A "bottom up" approach to validating particular judgments looks to rules that govern such judgments, and from rules to the principles from which they are derived. Four such principles are woven into

"commonsense" morality—an ethics that grows out of the nature of human beings, one that is simply put as "do good and avoid evil." The principles in question are as follows:

a. Respect for the autonomous choices of other persons (autonomy).
b. The obligation not to inflict harm intentionally (nonmaleficence).
c. Actions taken for the benefit of others (beneficence).
d. A fair, equitable, and appropriate distribution of goods in society (justice).

Critics of the principlist approach refer to its elements as a mantra (specifically, the *Georgetown Mantra*, because its authors—Robert Beauchamp and James Childers—were at Georgetown University when they articulated it) without substance; one that does not offer a schema for resolving conflict when more than one principle applies; a ritualistic incantation without a unifying, overriding theory to govern its use. When all is said and done, similar objections can be leveled against *any* ethical theory. The heart of the matter is to recognize the (ethical) problem and to admit with honesty which approach to solving it is used and why. In today's medical climate, however—when physicians have become *providers*, patients are now *clients*, and *any* cost is a *medical loss* to the insurance company (or governmental agency) that funds a *managed care* plan (see III.C.)—*any* of these theories, meant to guide ethical decision making in the practice of medicine, comes in conflict with the principles of *business* ethics. Those for whom the principles of business ethics are paramount have a primary fiduciary duty to the providers of capital—taxpayers, investors, and society at large—whose goals may be vastly different than those of traditional medicine. In a certain sense, the principle of justice comes to the fore in resolving these conflicts. Practical solutions (see III.C.) that preserve the essentials of the theory on which the physician's judgment and actions are based in any particular situation must be sought as a way out of such dilemmas.

II. CASE METHOD APPROACH TO CLINICAL ETHICS

John Fletcher and his associates developed a *case method approach* to the recognition and solution of ethical dilemmas that mimics standard decision making in medicine. The elements of the method are as follows:

A. Assessment. What is the nature of the medical problem and the relevant context in which it occurs? What are the options for therapy, their foreseeable risks and benefits, their short- and long-term prognoses, and the costs and resources (or mechanisms for payment) that are available? What do the patient, family, and surrogate decision makers *want*? What does the patient *need*, and what other needs may compete with that need? Are there any institutional, societal, or legal factors impinging on the patient or problem? What are the ethnic, cultural, and religious backgrounds from which the problems have arisen?

B. Identification of ethical problem(s). Which ethical problems, ranked in order of importance, are self-evident, and which are hidden? Which ethical theories are most relevant to such problems? Are there analogous cases in medicine or law, and if so, how so they apply? Which guidelines are most appropriate?

C. Decision making and implementation. What are the ethically acceptable options for solving the problems, and which are most acceptable? What justifications can be given for the preferred resolution of the problems? How can the preferred resolutions of the problem be accomplished? Is ethics consultation necessary or desirable? Is judicial review necessary or desirable?

D. Evaluation. This is an ongoing process that seeks to recognize missed opportunities and correct unworkable solutions. The process carries a preventive dimension that may propose changes in policy or provide educational opportunities to minimize the chance that similar problems will occur.

III. ETHICAL DECISION MAKING IN GENERAL

At the heart of any interaction between physician and patient is the matter of *who* decides *what* shall be done *when*. The physician brings to this interaction experience, knowledge, skill—and a set of personal values that may or may not be the same as, or even compatible

with, those of the patient. In years past, the physician's judgment ruled supreme. Today that judgment is tempered not only by a primacy of respect for the wishes of the patient, but also by the rules and regulations of various health care plans as well as by statutory and case law.

A. The primacy of the patient. A competent patient with the capacity for decision making can and should decide—even before the fact, anticipating the future through **advance directives** (e.g., "living will" and durable power of attorney for health care decisions ["health care proxies"]). Because many neurologic illnesses are chronic and inexorably disabling, often leaving the person without the capacity to decide, it is wise to introduce discussion of advance directives early in the course of caring for such a patient. Indeed, federal directives now *require* patients to be asked, on admission to hospital, whether they have executed, or wish to execute, an advance directive. A **bond of trust** should first be established, so that the patient does not interpret such discussions as a plan to abandon them at the end of life—an element of ethical decision making missing from the federal requirement. It is important to emphasize that decisions may change as a situation evolves.

B. Surrogate decision making. When capacity is lost, surrogates may be called upon to decide for the patient. Unless previously identified and appointed (in a health care proxy), the appropriate surrogate may be selected according to a hierarchy spelled out in state law. In extreme circumstances, a court-appointed surrogate may be necessary. Surrogates may strive to determine what the patient would have wanted (**substituted judgment standard**) or may try to decide what is best for the patient (**best interests standard**). The former standard is generally thought to be better, avoiding as it does conclusions made by one person (the surrogate) about another's (the patient's) "quality of life." Courts may require "clear and convincing evidence" of what it is the patient would have wanted under the circumstances in question. However, because such a scenario rarely exists in fact, and people often change their minds, requirements of this sort are most impractical. In all instances, it is wise to seek consensus and to continue to act in favor of life until that consensus is reached. It may take time to develop consensus, even when a surrogate has previously been appointed, especially when capacity is lost suddenly and without warning (e.g., after stroke). Physicians should be sensitive to the possibility of ulterior motives on the part of surrogates, fiscal, or otherwise.

C. "Managed care" plans. The spiraling cost of health care, among many contributing factors, has fueled an ongoing process of "health care reform"—much of which is basically about money. Because an immediate effect of health care decisions is the expenditure of money, a feature common to many proposals for such reform is a process requiring approval before decisions can be implemented. Sometimes the process has at its center a "gatekeeper"—often a primary care physician, who may be guided by situation-specific protocols. The rewards built into the system are keys to its ethical dimension. Under traditional fee-for-service medicine, the more a physician did, the more that physician was paid. Often under "managed care," the *less* a physician does, the *more* that physician is paid. The concept of "managed care" emphasizes the physician's obligation to *all* patients covered by a given plan—indeed, to society at large (i.e., putting the principle of **justice** foremost). If a physician hews to the primacy of the patient (the principle of **autonomy**) as the guiding principle in ethical decision making (see III.A.), *any* decision suggested by a physician and made by a patient should be made in the particular *patient's* best interest. No tests should be done, no treatment instituted, without that interest in the forefront of the physician's mind. If the system stands in the way of such decisions, physicians should oppose the system on behalf of their patients, vigorously—but fairly as well, not "gaming" the system with fabrications and the like. "Managed care" plans that reward physicians with incentives that limit or compromise care (e.g., by restricting the time that can be spent with a patient, denying access to appropriate consultants, and requiring the use of generic drugs when they may be less effective or more toxic) should be avoided.

To guide the physician through this narrow maze of ever-diminishing resources at a time of ever more complex and expensive options for diagnosis and therapy, the field of **evidence-based medicine** has developed. **Practice guidelines, critical pathways,** and similar approaches are being articulated from a wide range of sources. Physicians are well-advised to listen to and follow such approaches *unless* the approach is of the *gobsat* ("good old boys sitting around a table") variety.

IV. APPROACHES TO PARTICULAR PROBLEMS

A. "Brain death." An unwanted consequence of the development of more effective intensive care was the recognition that patients whose brains had suffered complete and irreversible loss of all brain function could continue to manifest adequate cardiovascular, renal, and gastrointestinal functions, as long as pulmonary function was supported by a ventilator. The *presence* of death—previously identified by the absence of heart action and breathing—could no longer be affirmed in such patients. This state of affairs called for the development of a new set of *criteria* by which the *presence* of death could be recognized—*not* for a new *definition* of death. Once those criteria are satisfied, the patient *is* dead—an unsettling conclusion for many to whom a warm body with a strong pulse and a chest moving in rhythm with a machine *cannot* be dead, *must* be asleep.

1. **"Whole brain" criteria.** Death of the *whole* brain is recognized in a normothermic body when loss of brain function results from an identifiable, irreversible, structural lesion, in the absence of sedative–hypnotic drugs or other, potentially reversible, metabolic conditions. Clinical examination for death of the whole brain requires the absence of brainstem reflexes (e.g., oculocephalic and ice water caloric stimulation evokes no eye movement; pupils are dilated and fixed to light; corneal responses are not present) and no ventilatory movement when the ventilator is stopped after a period of ventilation with 100% oxygen, even though the P_{CO_2} increases above 60 torr without ventilation. Recognition must be affirmed with a second examination, separated in time from the first by a variable interval, dependent on factors such as age and clinical cause. The interval may be specified by local statute or hospital policy. As with the use of cardiorespiratory criteria to recognize the presence of death, the patient is dead when the criteria are satisfied—that is, when the second examination affirms the findings of the first. A number of **confirmatory tests** are helpful when the clinical condition is compromised (e.g., when a patient has been in barbiturate coma after head injury) and may be required in certain circumstances (e.g., the patient is a child younger than 1 year). However, such tests are neither necessary nor sufficient to affirm the presence of death by themselves.
2. **"Brainstem" criteria.** In the UK, emphasis has been placed on the fact that the clinical examination on which the criterion of "brain death" is based looks only at the functions of the brainstem and not at whole-brain function. Higher cortical function is irrelevant in UK practice. This means that a person whose brainstem has irreversibly ceased to function but whose cerebral hemispheres are still working—a person with the so-called "locked in" syndrome—can be declared dead in the UK even though their cerebral hemispheres are still functioning. To the astute clinician, evidence of a working brain (in the form of eye movement, eyelid blinking, and the like) can usually be recognized, if one takes the time to look for it. However, in part because of this dilemma, many "brain death" policies and procedures in the US require a confirmatory test (e.g., isoelectric electroencephalography or cerebral angiography showing no flow within the cranium) to demonstrate that higher brain function is or must be absent to affirm the presence of "brain death."
3. **"Higher brain" death.** Certain philosophers (e.g., Robert Veatch) have called for a new *definition* of death, one holding that death is the permanent loss of that which is essential to the nature of a human being—consciousness and cognition. Prescinding from the difficulty of establishing the *criteria* by which death, so defined, might be recognized, certain practical problems arise when one considers the implementation of such a definition (e.g., can someone in the end stages of Alzheimer's disease, still breathing with normal vegetative function, be buried?).
4. **Ethical considerations.**
   a. **Telling the family.** Once the physician has recognized the presence of death using "brain death" criteria, the fact of that recognition should be conveyed to the family and others with ethical standing in those circumstances. The physician should be aware that statutory law (as in New Jersey) or Department of Health regulations (as in New York) may make allowance for the family to reject the use of "brain death" criteria on religious grounds—in which case the physician may be required to rely on traditional (cardiorespiratory) criteria in identifying the fact that death has occurred.

As in every interchange between physician and patient (including the extended patient-family and others), the physician should convey the fact gently, with compassion, and repeatedly until the fact is understood and accepted, if necessary. Although the family and others should not be burdened by being asked for permission to discontinue the ventilator (and thus, to allow cardiovascular death to ensue within a short time), the physician should be sensitive to reactions of denial and the like. The family should be given time to assimilate and accept the sorrowful fact of death. The physician should be sensitive to different ethnic and cultural heritages and to unresolved issues from the past, which can determine how long it will take for acceptance of that fact to occur. Terms such as *brain death* and *life support* should be avoided because they convey erroneous information. When someone *is* dead, the *person* is dead—not just the brain—and there is no longer any *human* life to support.

b. **After "brain death."** In addition to solving the problem of inappropriate and theoretically indeterminable use of a scarce resource (an intensive care bed), recognizing the death of a person whose body can continue to be kept "alive" permits a utilitarian calculus for the benefit of others. This is true in two instances—organ donation and the continued nurturing of an unborn child beyond the point of viability inside the body of a mother who has died. Permission for either action must be sought in the standard manner (see III.A. and B.). Considerations of **justice** weigh heavily in these situations. Different ethical theories come to different conclusions with regard to either action.

B. The "vegetative state." Although the condition is regarded by some as a "fate worse than death," a certain proportion of patients who have incurred overwhelming damage to their cerebral hemispheres (from anoxia after cardiac arrest or from massive traumatic brain damage or stroke) may—after a period of coma—evolve into a state of "wakefulness without awareness" accompanied by sleep–wake cycles and essentially intact brainstem and autonomic functions. Other patients may reach this state at the end of a chronic degenerative process. In 1994, a multisociety task force published its consensus on the clinical, diagnostic, and prognostic features of this condition—a consensus—a consensus with the particulars of which some physicians disagree, particularly because the task force did not acknowledge the concept of a "minimally conscious state" or deal with implications of the "locked-in" syndrome and other stops along the way from coma to full consciousness. At the heart of the matter is the issue of whether a patient in a "vegetative" (or any related) state is *truly unaware* of *all* stimuli and has no *conscious* thought; *when* the condition can rightly be regarded as *persistent* or *permanent*; and what, if any, impact may be had by a variety of therapeutic efforts and at what cost. Some regard these issues as incapable of anything but an arbitrary resolution. The task force deemed that any motor response of a patient in a "vegetative state" was primitive, random, or reflex, and as such, could not be interpreted as evidence of cognition. Further, the task force relied on imaging and pathologic studies, using modalities available at the time, as excluding any anatomic substrate for consciousness. Techniques such as functional MRI, single photon emission computed tomography, and so forth have called these judgments to question.

1. Withholding/withdrawing. It is generally accepted that patients with the capacity to decide for themselves are *not* obliged to accept *all* treatments, diagnostic studies, and the like, and may reject these even if one of the results of such rejection is death. With patients in the "vegetative state," such decisions devolve upon surrogates, duly identified (see III.B.). Most commonly, a burdens–benefit calculus is used to make a decision to reject. Such decisions should never be made with the *intent* of *causing* death but may be made even when the probability is that death will ensue. The obligations of the physician in this process are 3-fold: to reach medical certainty, as far as that is possible; to convey that certainty to the decision makers, as gently and as often as is necessary to ensure understanding and acceptance; and to respect and implement the decision, as long as that does not violate the conscience of the physician. From an ethical point of view, *withholding* is more problematic than *withdrawing*. Withholding does not give the patient the benefit of a therapeutic trial, even a time-limited trial. The physician does not know whether what might have been proposed would have helped the patient if it is not tried. It is imperative that all involved recognize (and behave accordingly with such recognition) that it is not *care* that is being withheld or withdrawn but rather

a burdensome treatment or diagnostic study without sufficient benefit for the patient. The natural tendency to avoid such patients, visit them less often, even not to speak (as though they might understand), should be steadfastly eschewed.

2. **Nutrition and hydration.** Given the deep meaning of food and water in human society, it is no wonder that some have balked at the withholding or withdrawing of these as symbolic of abandonment of the patient. Others have equated the food and water given to a patient in the "vegetative state"—generally through a gastrostomy tube, with all of its attendant paraphernalia and cost—with any other therapy that may be rejected (for reasons previously given), making such a decision to take that action more acceptable by use of the terms "artificial nutrition and hydration." Clearly, it is licit to reject such measures for the benefit of the patient—as when the *intent* is to minimize excess gastric or pulmonary secretions, incontinence, and the like. However, when the *intent* is to *cause* death, some regard that not as a benefit for the patient, but rather as the beginning of a "slippery slope" that would lead inexorably to the elimination of "absolutely worthless human beings." (Retarded children were referred to as "absolutely worthless human beings" in Nazi Germany.)
3. **Other considerations.** In making judgments about *level of care* of patients in the "vegetative state" or with other devastating, irremediable neurologic conditions, the physician is increasingly called upon to consider questions of **distributive justice.** These arise in such matters as access to intensive care, "managed care" decision, and even conservation of individual and group resources. Ethical physicians owe primary responsibility to their patients, unless both have knowingly entered into a contract with each other that permits limitation of care on such bases. That is not to demean the need to be in constant dialog with the patient or surrogate, in a gentle yet persistent effort to convince them of the reason of a considered position that may be different from theirs.

C. **Neurogenetic diseases.** There has been an explosion in the understanding of heritable neurologic disorders since 1983, when a marker for the gene for Huntington's disease was identified on chromosome 4.

1. **Diagnostic testing.** Research and commercial laboratories can provide the physician with DNA and non-DNA information helpful in the diagnosis of more than two dozen disorders of the central and peripheral nervous system (including various genetic forms of myopathy) with the likelihood that information about more diseases—and even such considerations as behavioral traits—will be available in the near future. Such testing may yield information pertinent not only to the diagnosis of an existing condition but also in the presymptomatic—even prenatal—situation, as well as with regard to carrier detection. Some—but by no means all—institutions use an extensive counseling system before and after testing, to ensure thorough, informed decision making for testing and appropriate support after results are made known to the patient or the guardian or surrogate.
2. **Ethical considerations.** Because the information garnered through diagnostic testing for neurogenetic disease in essence belongs to the persons being tested, it is important to their decision making that they understand all of the implications of testing and are prepared—with support from the physician—to deal with those implications. For example, knowledge that one is a carrier of a neurogenetic disease may allow for more responsible parenthood. Prenatal recognition that a neurogenetic disease is present in a developing infant may allow that infant's parents to prepare to shoulder the burden of that disease or to elect termination of the pregnancy. Because certain neurogenetic diseases (e.g., Huntington's disease) are associated with a higher rate of suicide than obtained in the population at large, presymptomatic diagnosis may enhance the risk of suicide, especially in a person who has experienced the ravages of the disease in an affected family member. Confirmation of the diagnosis of a neurogenetic disease may help the patient to cope with that disease because certainty is always easier to deal with than uncertainty. Caution must be expressed over the misuse of information from diagnostic testing—by employers and insurers (especially health care insurers), who might arbitrarily exclude persons with proven disease without reference to the impact (present or future) of the particular disease on specific job performance or to its call on pooled health care resources. With regard to the latter issue, competing considerations of **justice** may enter in and may require the person being tested to disclose the results of

testing. In the last analysis, the physician requesting the test as well as the person being tested should be aware of and informed about the various aspects of testing before proceeding with it. Genetic testing should never be done as part of the "routine" evaluation of a patient without such considerations being taken into account and explored.

3. **Gene therapy.** A promise for the future in neurogenetic disease is the hoped-for ability to insert or replace missing or defective genes in the cells of persons affected by such diseases. When the manipulation is directed at the affected cells, the procedure is termed **somatic cell therapy;** when it is directed at the initial fusion of sperm or ovum (or at those precursors of new human life themselves), it is termed **germ cell therapy.**

Somatic cell therapy raises issues common to research (see IV.F.). Germ cell therapy, with its implications for future generations, raises other considerations beyond the scope of this chapter. Mention should be made, however, of the proposed role of **stem cells** in this line of research. Stem cells, as the name implies, have the capacity of developing into any tissue (*totipotential*); many but not all tissues (*pluripotential*); or only some tissues (*unipotential*). They differ in *source* of derivation. Totipotential stem cells come from an embryo at the very earliest stage of development; pluripotential cells come from fetal tissue; and unipotential cells from adult tissue (e.g., bone marrow). The embryo and fetus do not survive harvesting of stem cells, so although the *goal* of stem cell development (e.g., cure of neurodegenerative diseases, repair of traumatic brain and spinal cord injury, cure of stroke, etc.) may be understandably laudable, the moral status of the *source* of stem cells cannot be ignored.

D. Static or progressive disorders with intact cognition. A spectrum of neuromuscular or spinal cord diseases have in common absence or loss of varying degrees of motor function (and hence—basically—of independence) with intact higher cortical function. Examples include spinal muscular atrophy, muscular dystrophy, and spinal cord dysraphisms (e.g., meningomyelocele), injuries, and other illnesses (e.g., multiple sclerosis [although mental functions may be impaired in multiple sclerosis]).

1. **Truth-telling.** Truth-telling becomes exceptionally painful for a physician when confronted with a healthy mind in a body now or predictably about-to-be robbed of its normal function. Maintaining hope and thwarting inevitable depression without making false and empty promises is an art not easily learned—and yet one whose reward is 100-fold from the patient and family, for whom life does, indeed, go on. Truth—though painful for physician and patient alike—is a reliable ally in the practice of this art. Physicians must be exceedingly sensitive to, and take time to care for, the emotional dimensions of the state in which their patients find themselves. As difficult as it may be not to do so, one must never abandon patients in this state. This is especially true in circumstances in which breathing becomes progressively more difficult.
2. **Problems at the end of life.** Despite all attempts at describing life on a ventilator, the patient may not be able to decide what that life might be like unless a trial of assisted ventilation is undertaken. After this point, the problem of withdrawing such assistance enters the scene. Minimizing suffering during withdrawal (e.g., with sedative–analgesic medications) runs the risk of suppressing what ventilatory function the patient still has. However, as long as the *intent* is the relief of that suffering and *not* to *cause* a more rapid demise, the use of such medication is appropriate (see IV.G.). In all such circumstances, physicians should call upon colleagues with complementing skills (such as nurses, social workers, physiotherapists, hospice workers, and the like) to help them implement the health care decisions reached by their patients, properly informed.

E. Static or progressive disorders with impaired cognition. Absence or loss of that which makes us uniquely human—consciousness and related higher neurologic functions—poses a number of dilemmas for the physician, who must deal with surrogates or even the courts in attempting to resolve those dilemmas. The paradigm clinical conditions range from anencephaly at one end of life to end-stage Alzheimer's disease at the other, with varying degrees of mental retardation and behavioral disorders—all of diverse causation—in between.

1. **Limiting medical interventions.** Until a new definition of death (see IV.A.3.) is accepted, persons with these conditions remain human beings—as difficult as it may be to recognize that fact at any given moment. One may argue whether some human beings have more of a right to use health care resources than others, but that is a societal decision that must not

be invoked at the bedside of a given patient by that patient's physician, absent agreement by the decision maker for that patient. On the other hand, the focus of decision making should properly be on compassionate *care*, not high-technology *cure*, once it is clear that one is dealing with a definitive, irreversible process.

2. **Making decisions.** Surrogate decision making according to a **substituted judgment** standard (see III.B.) is particularly problematic when the person has never had the capacity for independent judgment (e.g., an infant with anencephaly, or a person of any age with severe mental retardation). A sorry chapter in US jurisprudence in this regard dealt with involuntary sterilization—justified by the alternate, more subjective, **best interests** standard. The latter standard often is used in dealing with unwanted, sometimes self-injurious, behavior by means of medication, restraints, institutionalization, and the like—even "psychosurgery." Extreme caution must be the rule, and compassion the guide. The use of **advance directives**—particularly the appointment of someone to hold a **durable power of attorney for health care decisions**—is critical to the goal of making decisions when patients can no longer articulate their own decisions. Physicians who care for patients with neurodegenerative disorders (in particular) are well-advised to encourage their patients to consider and implement advance directives earlier rather than later, involving friends and family in discussions that will make possible valid substituted judgments, when and if those become necessary, well *before* their patients lose the capacity for truly informed decision making.
3. **Involvement of family.** Family members and others bearing responsibility for the care of persons without the capacity to decide for themselves should be intimately involved with decision making in this category, unless there is a valid reason for them not to be involved. When capacity has been present and is now lost (as in the end stages of Alzheimer's disease), attention should be paid to health care proxies if previously executed. It must be borne in mind that people change their minds, especially as circumstances change. Few of us can *truly* be aware of what it is like to become demented, nor can we truly know what it is we would decide for ourselves if and when we were to reach such a state. The burden of dementia is on those who care for the demented, not on the demented themselves.

F. Research in neurology. Dr. Labe Scheinberg once described the practice of neurology with the aphorism, "diagnose—then adios!" at a time when there were few, if any, effective treatments for neurologic disease. The last decade of the 20th century was deemed the "Decade of the Brain" because of the remarkable advances in the understanding and management of neurologic disease that began to come forward during that time. The move from Scheinberg's aphorism to a brave and wonderful new world occurred in large measure because of research—often involving human subjects early (because no appropriate animal model existed), often with great risk (in searching for an elusive benefit), and often raising the spectra of a conflict of interest (between physicians caring for patients and conducting meaningful research by enrolling those patients in controlled clinical trials).

1. **Valid versus invalid research.** The *sine qua non* of valid research is peer review—approval of a research proposal by a thoughtful, responsible, knowledgeable group of peers to judge the question as worthy of being asked; the answer as likely to be forthcoming; and the hoped-for benefit as worth the predicted risk. The availability of external funding makes it possible to conduct approved research honestly and openly, without employing the subterfuge of paying for research under the guise of acceptable patient care. The process that effects valid research involves institutional review boards and other oversight bodies to ensure validity at every step along the way.
2. **Consent issues.** Persons with devastating illnesses (e.g., most neurologic diseases) are particularly vulnerable to any offer of hope, even when that offer wears the cloak of a research hypothesis. The offer of hope may come in the form of a controlled clinical trial, in which the decision as to which treatment (e.g., active treatment for placebo) the patient is to receive is made by the parameters of the trial, not by the patient's physician. Physicians who refer their patients for enrollment in such a trial must do that with **clinical equipoise**—meaning that they must agree that the trial is necessary; that there is not, as yet, any proven approach that would guarantee benefit to their patient (for if there is, their patient cannot be denied access to that—which may mean a more cumbersome, likely less valid, trial of the unproven therapy); and that the risks of the

trial are balanced by the benefits their patient can expect. If there is no expected benefit to patients, then—at the very least—society should benefit from the expected gain in knowledge that will come from the trial. Consent is especially problematic for children and for others without the capacity to give their own consent. Some have gone so far as to take the position that nontherapeutic research involving patients should never be done, whereas others emphasize a broader debt to society that can only be paid by advancing knowledge through valid clinical research.

G. Chronic pain. Diverse neurologic conditions are commonly associated with pain, often requiring hefty doses of potent analgesics for relief—doses of medications that may suppress respiration, lower blood pressure to dangerous levels, and have other unwanted effects. The ruling principle here is that of the **double effect**—the unwanted (indirect, merely permitted) effects (in this instance, possible aspiration or even death) are allowed, as long as the primary (direct, intended) effect (in this instance, relief of pain and suffering) is desirable, and cannot be achieved in any other way. It is important to remember that pain can be physical and identifiable, or metaphysical and existential. Adequate relief of both kinds of pain is at the heart of **comfort care,** which can be chosen by patients at any stage of their lives, especially at the end of a terminal illness. In this regard, **hospice** may be an ideal setting in which to provide such care (although the trajectory of neurologic illness often exceeds the arbitrary limits set by Medicare and other funding agencies for the provision of hospice care).

V. INTERFACE WITH THE LAW

Many of the most notable, landmark legal decisions involving patient decision making have dealt with patients with neurologic problems. In the matter of surrogate decision making with regard to the withholding or withdrawal of medical treatment, *Quinlan* and *Saikewicz* set the standard of substituted judgment for once-competent and never-competent patients, respectively. *Conroy* affirmed the fact that autonomy remains intact, even when a person is no longer able to assert that right or even appreciate its effectuation. *Cruzan* acknowledged the right of states to require stringent ("clear and convincing") evidence of the prior wishes of a once-competent person as applicable to his or her current status. The physician should be aware of such cases and should try to discern their relevance to the situation at hand (see II.B.). The physician should recognize that the impact of such cases (in terms of setting precedent) is limited to the jurisdiction in which the decision was rendered but may (in terms of argument) be of probative value in other jurisdictions.

VI. REFERRALS

Most ethical dilemmas can (and should) be dealt with by physicians with colleagues (nurses, social workers, clergy, and the like) in the care of their patients—perhaps with the help of **ethics consultation** and the awareness of hospital administration and attorneys. In solving such dilemmas, physicians should keep the general principles of decision making, truth-telling, and involvement of family (see III.A. and IV.F. in particular) in mind at all times. Physicians should not hesitate to seek the guidance and assistance of senior, more experienced clinicians in dealing with these issues at a practical level. Generally, recourse to the courts should be a last resort, because the legal process takes an interminable length of time and often is not sensitive to the important nuances of a particular situation.

Recommended Readings

American Academy of Neurology Code of Professional Conduct. *Neurology* 1993;43:1257 (revisions available on the AAN website).

American Medical Association Council on Ethical and Judicial Affairs. *Code of Medical Ethics: Current Opinions and Annotations, 2010–2011.* Chicago, IL: American Medical Association.

Beauchamp TL, Childress JF. *Principles of Biomedical Ethics*. 4th ed. New York, NY: Oxford University Press; 2008.
Bernat JL. *Ethical Issues in Neurology*. 3rd ed. Boston, MA: Butterworth-Heineman; 2008.
Fletcher JC, Lombardo PA, Spencer E. *Fletcher's Introduction to Clinical Ethics*. 3rd ed. Frederick, MD: University Publishing Group; 2005.
Giordano JJ, Gordijn B, eds. *Scientific and Philosophical Perspectives in Neuroethics*. New York, NY: Cambridge University Press; 2010.
In re Quinlan, 70 N.J. 10, 355 A.2d 647, *cert. denied sub nom. Garger v. New Jersey*, 429 U.U. 922, 1976.
Jennett B. *The Vegetative State. Medical Facts, Ethical and Legal Dilemmas*. New York, NY: Cambridge University Press; 2002.
Lo B. *Resolving Ethical Dilemmas. A Guide for Clinicians*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
Wijdicks EFM, ed. *Brain Death*. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.

CHAPTER 36

Ischemic Cerebrovascular Disease

José Biller

Cerebrovascular disease comprises a heterogeneous group of disorders that herald their presence by producing symptoms and signs resulting from either **ischemia** or **hemorrhage** within the CNS. The term **stroke** is most commonly used by both physicians and the general public to refer to any one of this diverse group of disorders. It connotes the notion that onset of symptoms is abrupt and leaves a lasting physical or cognitive disability. An ischemic stroke is an acute **brain attack** caused by the interruption of blood flow within one or more arterial territories of the brain.

Stroke is currently the second most common cause of death worldwide, and a primary cause of long-term disability in much of the industrialized world. Cerebrovascular disease is also the most common neurologic condition necessitating hospitalization. Patients surviving a transient ischemic attack (TIA) or ischemic stroke are at increased risks of recurrent ischemic events and have a reduced life expectancy.

There are two main types of strokes—ischemic and hemorrhagic. The focus of this chapter is to outline the general approach to the diagnosis and management of ischemic stroke.

Of the 795,000 new or recurrent strokes in the United States each year, approximately 87% result from **cerebral infarction.** On average, someone in the United States has a stroke every 40 seconds, and someone dies of a stroke every 4 minutes. Ischemic stroke may result from (1) large-artery atherosclerotic disease, (2) small-artery disease (lacunes), (3) cardioembolism, (4) hemodynamic (watershed) infarction, (5) nonatherosclerotic vasculopathies, (6) hypercoagulable disorders, or (7) infarction of undetermined causation.

Ischemia sets in motion a cascade of biochemical alterations leading to lactic acidosis, influx of calcium and sodium, and efflux of potassium that culminates in cell death. The pathogenesis of ischemic strokes can be conceptualized as a permanent lack of blood flow to a focal region of the brain, depriving it of needed glucose and oxygen. Normal **cerebral blood flow (CBF)** to the adult brain is 50 to 55 ml per 100 g per minute. The threshold for synaptic transmission failure occurs when CBF decreases to approximately 8 to 10 ml per 100 g per minute. At this level, neuronal death can occur. The brain region with a CBF level from 8 to 18 mL per 100 g per minute sometimes is called the **ischemic penumbra.** Rational treatment of patients with ischemic cerebrovascular disease depends on accurate diagnosis. Most interventional strategies aim to promote rapid perfusion of brain tissue and to treat the complications of **brain swelling** postischemic stroke.

The cause of an ischemic stroke must first be established through an expeditious but careful history-taking, detailed physical examination, and paraclinical investigations. A basic evaluation, to be performed for all patients with ischemic stroke, includes complete blood cell count with differential and platelet count, erythrocyte sedimentation rate, prothrombin time (PT), activated partial thromboplastin time (aPTT), plasma glucose level, blood urea nitrogen, serum creatinine, lipid analysis, urinalysis, chest radiography, and electrocardiography. Creatine kinase (CK) and CK MB fraction and cardiac troponins provide evidence of a concurrent myocardial infarction (MI).

CT should also be performed on all patients because it may depict hemorrhagic lesions that can mimic an ischemic stroke. If cerebellar or brainstem symptoms are present, imaging should include thin cuts through the posterior fossa. MRI is superior to CT in evaluation for cerebral ischemia (Fig. 36.1). MRI with diffusion-weighted imaging (DWI) is useful to delineate ischemic strokes. MRI with DWI or perfusion-weighted imaging is useful to visualize the **ischemic penumbra** (Fig. 36.2). Computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) complements the information obtained

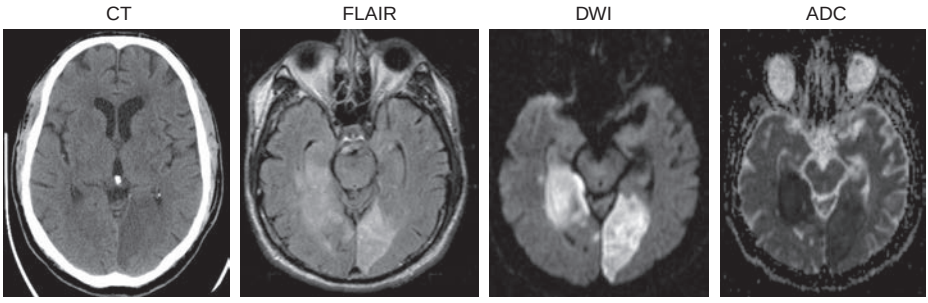

FIGURE 36.1 A 69-year-old man had new onset of right-sided visual blurring and right-sided numbness. Neuroimaging studies demonstrate left occipital and right medial temporal infarcts; the right side temporal infarct was harder to be visualized on CT. (Courtesy of Dr. Lotfi Hacein-Bey.)

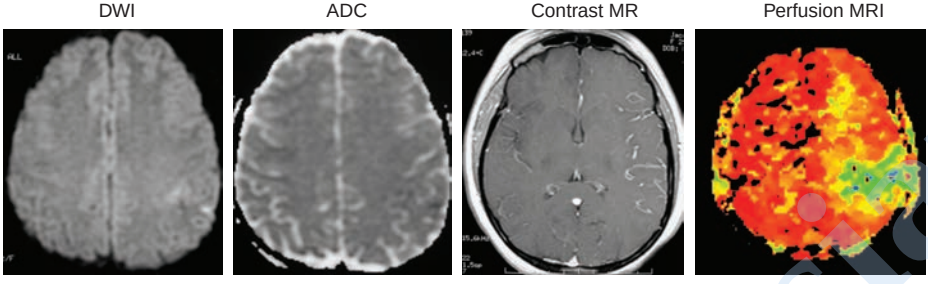

FIGURE 36.2 Perfusion/diffusion mismatch. Acute left ICA occlusion in a 29-year-old woman. There are very small diffusion defects in the left posterior frontal lobe. Perfusion MRI shows that the full left MCA territory is at risk. (Courtesy of Dr. Lotfi Hacein-Bey.)

with MRI and frequently delineates the pathoanatomic substrate of the stroke. Gadolinium enhanced multicontrast-weighted MRI may also allow accurate quantification of carotid artery plaque instability. CT perfusion is also useful to visualize the ischemic penumbra. The emphasis in screening should be on noninvasive testing including carotid duplex ultrasound and transcranial Doppler ultrasound. Carotid duplex ultrasound is often obtained when clinical manifestations could be attributed to carotid artery disease. Increased plaque echolucency has been associated with higher risks of stroke and TIA. Transcranial Doppler ultrasound identifies high-risk patients with sickle cell anemia, indirectly assesses cerebral perfusion reserve, and may also enhance the effect of ultrasound on thrombolysis.

Cardiac investigations to determine whether emboli have cardiac sources are advised in selected circumstances. Two-dimensional echocardiography for older patients with ischemic stroke is limited to patients with clinical clues of heart disease. Two-dimensional echocardiography should be considered for all patients younger than 45 years with otherwise unexplained ischemic stroke. Transesophageal echocardiography should be used for selected individuals, particularly for evaluation of mitral and aortic prosthetic valves or vegetations, whenever there is a need for better visualization of the left atrial appendage or interatrial septum, or when a right-to-left shunt is suspected.

Most patients with ischemic stroke have extracranial or intracranial **cerebrovascular atherosclerosis.** Cerebrovascular atherosclerosis primarily affects the carotid bulb, carotid siphon, middle cerebral artery (MCA) stem, origin, and intracranial segments of the vertebral arteries, and basilar artery. Ischemia results from thrombotic vascular occlusion, embolization of atherosclerotic debris, or hemodynamic disturbances causing focal hypoperfusion in areas in which the circulation is inadequate.

I. NATURAL HISTORY AND PROGNOSIS

A. Ischemic stroke resulting from large-artery atherosclerotic disease. Large-artery atherothrombotic infarctions almost always occur in patients who already have significant risk factors for cerebrovascular atherosclerosis, such as arterial hypertension, cigarette smoking, diabetes mellitus, dyslipidemia, asymptomatic carotid bruits, asymptomatic carotid stenosis, and TIAs.

1. A **TIA** is defined as a transient episode of neurologic dysfunction caused by focal brain or retinal ischemia without infarction. The conventional boundary in differentiating between a TIA and stroke has been 24 hours. Yet, most TIAs last only a few minutes. TIAs are most often caused by thromboembolism associated with large artery atherosclerosis, cardioembolism, or small vessel (lacunar) disease. TIAs are important harbingers of subsequent stroke and are often associated with lesions on brain imaging. TIAs involving the anterior or carotid circulation should be distinguished from those involving the posterior or vertebrobasilar circulation.
   a. The following symptoms are considered typical of TIAs in the **carotid circulation:** ipsilateral amaurosis fugax, contralateral sensory or motor dysfunction limited to one side of the body, aphasia, contralateral homonymous hemianopia, or any combination thereof.
   b. The following symptoms represent typical TIAs in the **vertebrobasilar system:** bilateral or shifting motor or sensory dysfunction, complete or partial loss of vision in both homonymous fields, or any combination of these symptoms. Isolated diplopia, vertigo, dysarthria, and dysphagia should not be considered TIAs, but in combination with one another or with any of the symptoms just listed, they should be considered vertebrobasilar TIAs.
   c. Preceding TIAs occur in approximately 30% to 50% of patients with atherothrombotic brain infarction, in 15% to 25% of lacunar infarctions, and in 10% of cardioembolic infarctions.
   d. A TIA is a risk factor for stroke. The independent risk of a subsequent stroke is at least three times greater for patients with histories of TIAs than for those who have not had TIAs. The **ABCD2** score is useful for stroke risk stratification in patients with TIAs: **A**ge > 60 years = 1 point; **B**lood pressure > 140/90 mm Hg = 1 point; **C**linical unilateral weakness = 2 points; speech-only impairment = 1 point; **D**uration > 60 minutes = 2 points, < 60 minutes = 1 point; **D**iabetes = 1 point. Scores of 4 or greater in the **ABCD2** score indicate moderate to high-stroke risk.
2. **Atherosclerosis** tends to occur in areas of reduced flow shear such as the posterior aspect of the carotid artery bulb. It primarily affects the larger extracranial and intracranial vessels. Approximately 80% of ischemic strokes occur in the **carotid or anterior circulation,** and 20% in the **vertebrobasilar or posterior circulation** (Fig. 36.3).
3. The mechanism of large-artery atherothrombotic infarction is either **artery-to-artery embolization** or **in situ formation of a thrombus** in the setting of preexisting arterial stenosis. Artery-to-artery embolism or low-CBF is a common mechanism of cerebral ischemic events. Embolism from ulcerated carotid atherosclerotic plaques is the most common cause of cerebral infarction. In situ thrombosis occurs in the proximal carotid, distal vertebral, and basilar arteries. Such a circumstance may arise in association with hypercoagulable states. When the internal carotid artery (ICA) occludes, it can also cause low-flow ischemic events depending on status of the collateral circulation.

B. Ischemic strokes resulting from small-vessel or penetrating artery disease (lacunes). Long-standing arterial hypertension affects primarily the smaller penetrating intracranial vessels. It induces hypertrophy of the media and deposition of fibrinoid material into the vessel wall (fibrinoid necrosis), which eventually leads to occlusion. **Lacunes** are small ischemic infarcts in the deep regions of the brain or brainstem ranging in diameter from 0.5 to 15.0 mm resulting mainly from lipohyalinosis of penetrating arteries or branches related to long-standing arterial hypertension—chiefly the anterior choroidal, middle cerebral, posterior cerebral, and basilar arteries. Diabetes mellitus and extracranial arterial and cardiac sources of embolism are found less frequently.

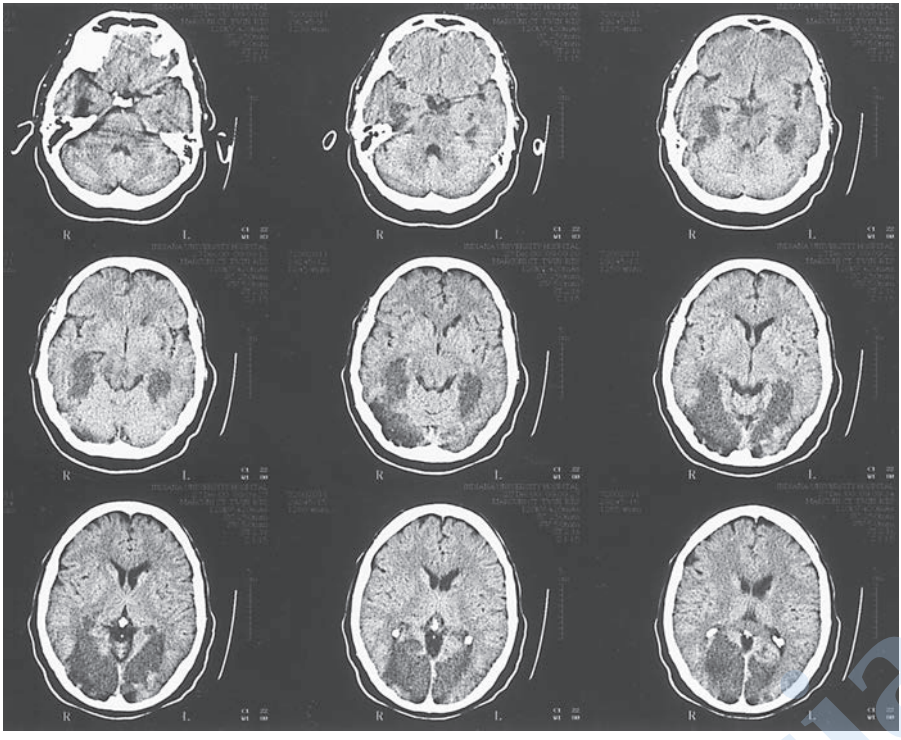

FIGURE 36.3 Axial unenhanced CT shows areas of low attenuation involving the medial aspects of both temporal lobes, both occipital lobes, the midbrain, and the pons in a patient with a diagnosis of basilar arterial occlusion.

TABLE 36.1 Cardiac Sources with High-Risk Embolic Potential

Atrial fibrillation
Acute MI
Mechanical prosthetic heart valves
Rheumatic mitral stenosis
Dilated cardiomyopathies
Infective endocarditis
Atrial myxomas

C. Ischemic stroke resulting from cardioembolism. Cardioembolic strokes are associated with substantial morbidity and mortality. Embolism of cardiac origin accounts for approximately 15% to 20% of all ischemic strokes. Emboli from cardiac sources frequently lodge in the MCA territory, often are large, and often have the worst outcomes. Although most types of heart disease can produce cerebral embolism, certain cardiac disorders are more likely to be associated with emboli (Table 36.1). Low or uncertain embolic risk disorders include mitral valve prolapse, mitral annulus calcification, aortic valve calcification, calcific aortic stenosis, bicuspid aortic valve, atrial flutter, patent foramen ovale, atrial septal aneurysms, valvular strands, and a Chiari network. Identification of a cardiac source of potential embolism is helpful for management. However, finding a potential cardiac embolic source is not by itself sufficient to diagnose embolic cerebral infarction because many cardiac problems can coexist with cerebrovascular atherosclerosis.

D. Ischemic stroke resulting from hemodynamic mechanisms. Another mechanism of ischemic CNS damage is decreased systemic perfusion pressure that causes diminished

blood flow to the brain in a diffuse manner. This occurs most commonly in the setting of cardiac pump failure or systemic hypotension. **Border-zone** ischemia often is explained by the combination of two frequently interrelated processes—hypoperfusion and embolization. This type of insult is most critical in border-zone territories, or so-called watershed areas, in the most distal regions of supply of the major arterial territories. Border-zone ischemia can result in several characteristic syndromes depending on whether the ischemia is in the border-zone territory of all three major arterial systems (anterior, middle, and posterior cerebral arteries), the territory between the anterior and middle cerebral arteries, or the territory between the middle and posterior cerebral arteries. **Watershed infarcts** often are bilateral, but can be unilateral when preexisting ipsilateral vascular disease causes focal hypoperfusion in the most distal territory. Other mechanisms whereby watershed infarcts develop include microemboli and hematologic abnormalities.

E. Ischemic stroke resulting from nonatherosclerotic vasculopathies. Several nonatherosclerotic forms of vasculopathy are predisposing factors for ischemic stroke. These vasculopathies include, among others, cervicocephalic arterial dissection (Fig. 36.4), Moyamoya, fibromuscular dysplasia, and cerebral vasculitis. Together, these uncommon conditions represent 5% of all ischemic strokes. They are relatively more common among children and young adults.

F. Ischemic stroke resulting from hypercoagulable disorders. Alterations in hemostasis have been associated with an increased risk of ischemic stroke. These conditions include deficiencies in the anticoagulant proteins such as antithrombin, protein C, protein S, activated protein C resistance, factor V Leiden mutation, prothrombin gene (G20210A) mutation, and heparin cofactor II; disorders of fibrinogen or of the fibrinolytic system; methylene-tetrahydrofolate reductase (MTHFR) gene mutation (particularly the MTHFR 677TT polymorphism); lipoprotein (a) disorders; and secondary hypercoagulable states encountered in patients with malignancies, pregnancy/puerperium, the antiphospholipid antibody syndrome, nephrotic syndrome, polycythemia vera, sickle cell disease, thrombotic thrombocytopenic purpura (TTP), and paroxysmal nocturnal hemoglobinuria. These disorders account for 1% of all strokes and for 2% to 7% of ischemic strokes in young patients.

G. Ischemic stroke of undetermined causation. Despite extensive evaluation, in as many as one-third of ischemic strokes, a cause cannot be determined. This percentage is possibly higher among patients younger than 45 years. It is possible that some of these strokes are caused by cardioembolic or hematologic events not readily demonstrable.

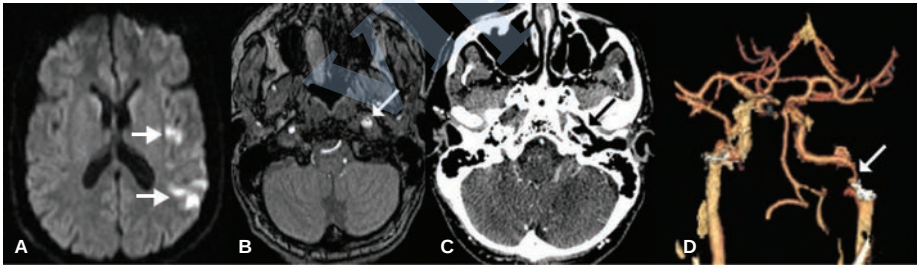

FIGURE 36.4 A 47-year-old man with acute onset of aphasia and right upper extremity weakness from left hemispheric ischemic injuries demonstrated on DWI MRI (**A,** *arrowheads*). Source image from MRA shows enlargement of the left ICA immediately inferior to the petrous canal (**B,** *arrow*) due to aneurysmal dilatation of the false lumen by an intimal flap. CTA, axial image (**C**) and three-dimensional reconstruction (**D**) show the same findings.

II. PREVENTION

The prevention of strokes follows three main avenues—control of modifiable risk factors, pharmacologic therapy, and surgical intervention. Knowledge and control of modifiable risk factors are paramount in prevention of primary and secondary strokes. Treatable or modifiable risk factors include arterial hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, excessive alcohol intake, obesity, and physical inactivity. Other risk factors include age and gender, cardiac disease, TIAs, previous strokes, asymptomatic carotid bruit or stenosis, high hemoglobin level or hematocrit, increased fibrinogen level, use of oral contraceptives, and possibly race and ethnicity.

A. **Hypertension** predisposes to ischemic stroke by aggravating atherosclerosis and accelerating heart disease. Approximately, 60 million Americans have arterial hypertension. Arterial hypertension is the most important modifiable risk factor for stroke, increasing the relative risk 3- to 4-fold. Blood pressure lowering also reduces the risk of stroke in individuals with isolated systolic hypertension and in elderly subjects. Blood pressure treatment resulting in a decrease in mean diastolic blood pressure of 5 mm Hg over 2 to 3 years is associated with a 40% reduction in risk of stroke. Blood pressure targets are individualized according to age, ethnicity, and coexisting comorbidities. Reduction of blood pressure is more important than the specific antihypertensive agent or modality use.

B. **Diabetes mellitus** increases the risk of ischemic cerebrovascular disease 2- to 4-fold compared with the risk among persons without diabetes. In addition, diabetes increases morbidity and mortality after stroke. Most persons with diabetes die of atherosclerotic cardiovascular complications, and atherosclerosis causing blockage to the arteries in the heart and brain accounts for >80% of all deaths in diabetes. Rigorous blood pressure control is particularly recommended for diabetic patients. Patients with diabetes who have concomitant hypertension should be treated with a regimen that includes an ACE inhibitor or an angiotensin receptor blocker. There is presently no evidence to suggest that tighter diabetic control decreases the risk of stroke or recurrent stroke.

C. **Cigarette smoking** is an independent risk factor for ischemic stroke among men and women of all ages. More than 5 years may be required before a reduction in stroke risk is observed after cessation of smoking.

D. **Hyperlipidemia.** There is a positive association between serum cholesterol and risk of ischemic stroke. Patients with TIAs or ischemic stroke with elevated cholesterol, comorbid coronary artery disease, or evidence of an atherosclerotic lesion should be managed with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG Co-A) reductase inhibitors (statins). The statins block the rate limiting step in cholesterol biosynthesis. These agents not only effectively lower the rate of cholesterol biosynthesis, but a number of cholesterol independent or pleiotrophic effects allow statins to exert important influences on a number of critical cellular signaling mechanisms. Meta-analysis of randomized trials of statins in primary or secondary preventions has shown a relative stroke risk reduction of approximately one-fifth. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels, treatment with atorvastatin 80 mg daily significantly reduced the risk of nonfatal or fatal stroke, and the risk of stroke or TIA compared with placebo. A reduction in major cardiovascular events was also observed. Although atorvastatin was associated with fewer ischemic strokes than placebo, hemorrhagic strokes were more frequent in the atorvastatin-treated group. Further data are needed regarding the effective range of HMG Co-A reductase inhibitors doses in these patients.

E. **Excessive alcohol use.** There is a J-shaped association between alcohol consumption and ischemic stroke. Lower doses (up to two drinks a day) offer reduced risk and higher doses elevate the risk. Moderate alcohol intake may elevate high-density lipoprotein concentration.

F. **Obesity and physical inactivity.** Obesity exerts an independent increase in risk of stroke among men younger than 63 years. This increase is greater among cigarette smokers and patients with hypertension, elevated blood glucose, or hyperlipidemia. There is some evidence that physical activity can reduce the risk of stroke.

III. TREATMENT

Ischemic stroke is a medical emergency. Any patient with acute ischemic stroke should be admitted to hospital for prompt evaluation (Table 36.2) and treatment. This is best accomplished in an intensive care unit or stroke unit. Management must be individualized according to the pathophysiologic process.

A. General measures. Particular attention should be paid to the following parameters (Table 36.3).

1. Medical measures

a. **Respiratory tract protection and infection.** The airway of an obtunded patient should be protected. Some critically ill patients need ventilatory assistance. Aspiration and atelectasis should be prevented. **Nosocomial pneumonia** frequently complicates stroke and is a leading cause of mortality in the second to fourth weeks following cerebral infarction. Risk factors for nosocomial pneumonia include advanced age, prolonged hospitalization, serious medical comorbidity, immunosuppression, and endotracheal intubation.

Dysphagia is common after stroke. Failure of the swallowing process increases the risks of aspiration, malnutrition, and dehydration. The risk of pneumonia is increased by aspiration, which occurs in as many as 25% of unilateral hemispheric strokes and 70% of bilateral hemispheric or brainstem strokes. A meticulous history and examination of the oral, pharyngeal, and esophageal stages with a modified barium swallow using videofluorography are recommended. Oral ingestion of food or liquids often is precluded in the first 24 to 48 hours. Nasogastric feedings often are necessary. Some patients may need a gastrostomy to maintain adequate nutritional intake.

b. **Urinary tract infections.** Urinary bladder dysfunction can complicate stroke, particularly basal ganglia, frontoparietal, and bilateral hemispheric strokes. Urinary tract infections are an important cause of hyperpyrexia following stroke. They contribute to almost one-third of stroke-related deaths and are present in almost one-half of patients in autopsy series. Incontinent or comatose patients should be catheterized, preferably with a condom catheter for men or a closed Foley's catheter for women. Many patients need an indwelling catheter, which is associated with a risk of infection. In addition, even continent patients can have postvoiding residuals that also increase the likelihood of urinary tract infections.

c. **Electrolytic and metabolic disturbances**

(1) **Electrolytic disturbances.** Stroke patients are at risk of electrolyte disturbances resulting from reduced oral intake, potentially increased gastric and skin losses,

TABLE 36.2 Stroke Evaluation Targets for Potential Thrombolysis Candidates: NINDS Guideline Recommendations

Time Interval	Time Target
EMS transport from home ED	10 min
Time from arrival in ED to availability of neurological expertise	15 min (phone or physical presence)
Time from arrival in ED to completion of head CT	25 min
Time from arrival in ED to completion of CT interpretation	45 min
Time from arrival in ED to treatment with thrombolytics	60 min
Time from arrival in ED to admission in monitored bed	3 hr

Abbreviation: ED, emergency department.

TABLE 36.3 Areas of Emphasis in General Medical Measures

Respiration	Hospital-acquired infection
Blood pressure	VTE
Fluids and electrolytes	Seizures
Skin care	Spasticity
Dysphagia, aspiration	Depression
Urinary dysfunction	

and derangements in secretion of antidiuretic hormone (ADH). Levels of ADH increase after stroke. In some cases, inappropriate secretion of ADH places the patient at risk of hyponatremia. Possible mechanisms include damage to the anterior hypothalamus and a prolonged recumbent position. In most cases, these alterations do not persist beyond the first week after a stroke.

(2) **Hyperglycemia** in acute stroke is a common phenomenon and correlates with a poor outcome. Hyperglycemia increases the extent of ischemic brain damage. High-serum glucose levels increase anaerobic metabolism, increase lactic acid production in ischemic brain tissue, and cause cellular acidosis. Hypotonic solutions or fluids containing glucose should be avoided.

d. **Venous thromboembolism** (VTE) is a common complication among patients with acute ischemic stroke. The risk is highest in the early weeks after ictus, but remains significant in the chronic phase. The frequency of **deep venous thrombosis** (DVT) ranges from 20% to 40% in hospitalized stroke patients, and approximately 75% of stroke patients may develop DVT without prophylaxis. Moreover, lethal pulmonary embolism may account for up to 25% of the early poststroke deaths. Prophylaxis of VTE is an essential component of stroke center protocols. Prevention includes the use of pressure gradient stockings, pneumatic compression stockings, low-dosage subcutaneous unfractionated heparin (UFH) (5,000 units every 8 to 12 hours), or low-molecular-weight heparin (Enoxaparin 40 mg once daily, Dalteparin 5,000 units once daily, or Tinzaparin 4,500 units once daily).

e. **Cardiac events** constitute an important cause of death after acute stroke because 40% to 70% of these patients have baseline **coronary artery disease.** Cardiac manifestations that can occur after acute ischemic stroke include ECG abnormalities, cardiac arrhythmias, elevation of CK-MB or cardiac selective troponin levels, left ventricular dysfunction, and MI. Approximately 15% of deaths following ischemic stroke are from fatal arrhythmia or MI. As many as 30% of patients have ST segment depression on an ECG in the first 48 hours after the event, and 35% have ventricular couplets or tachycardia. Other changes include QT interval prolongation, T-wave inversion, or increases in duration and amplitude of T waves. Strokes restricted to the insular cortex have been associated with arterial hypertension, cardiac arrhythmias, increased risk of myocardial injury, raised catecholamine levels, and an increased susceptibility to sudden death.

f. **Cerebral autoregulation** is lost during acute ischemic stroke. The blood pressure should be measured frequently during the first few days after ischemic stroke. Transient blood pressure elevation following acute cerebral infarction and normalization over days without treatment are common. Mild to moderate hypertension may be compensatory, and rapid lowering of the blood pressure is generally not recommended. Exceptions to this rule include patients with hypertensive encephalopathy and cerebral ischemia secondary to aortic dissection.

g. **Pressure sores.** Stroke patients, like other patients with reduced mobility, are at increased risk of having pressure sores. Altered level of consciousness, peripheral vascular disease, and malnourishment are contributing factors. Pressure sores develop most often over bony prominences—sacrum, ischium, trochanters, and the areas around the ankles and heels. The patient's position should be changed frequently to reduce pressure and shear forces. Flotation beds help reduce the risk. Treatment includes debridement and moist dressing. Surgical treatment sometimes is necessary. Cellulitis in the surrounding skin and systemic infection necessitate antibiotic therapy.

h. **Depression.** Depression occurs in the first few weeks after stroke, but is maximal between 6 and 24 months afterward. Patients with left frontal strokes appear to be more susceptible than are those with right hemisphere or brainstem strokes, but this remains debatable. Depression also correlates with severity of neurologic deficit and quality of available social support. Therapy for poststroke depression is the same as that for endogenous depression.

2. **Neurologic measures.** Approximately 30% of patients with acute ischemic strokes worsen after the initial event, but deterioration after stroke or "stroke in evolution"

does not necessarily equate to propagating thrombus or recurrent embolism (Table 36.4). Massive hemispheric infarctions have a high mortality. Large (malignant) MCA territory strokes (5% of all strokes) are associated with poor prognosis. The underlying mechanism of malignant MCA infarction is often either a carotid terminus occlusion or a proximal MCA occlusion. Acute cerebellar infarction may cause brain stem compression with hydrocephalus.

a. **Brain edema** is the most common cause of deterioration and early death during the first week after acute cerebral infarction. Young patients and patients with large infarcts are most affected. Massive **cerebral edema** complicates approximately 10% of large hemispheric strokes. Edema develops within several hours after an acute ischemic brain insult and peaks around 3 to 5 days. **Ischemic brain edema** is initially **cytotoxic** and later **vasogenic.** Cytotoxic edema involves predominantly the gray matter, whereas vasogenic edema involves predominantly the white matter. No specific pharmacologic agent has been proved effective against ischemic cerebral edema. Corticosteroids have not been proved useful in the management of ischemic cerebral edema and may even be detrimental. Mannitol does not cross the **blood–brain barrier** and may accentuate compartmentalized pressure gradients between abnormal and normal brain regions. Hypernatremia, hypokalemia, and hypocalcemia can result from excessive osmotherapy. Excessive osmotherapy can also result in intravascular volume depletion and arterial hypotension. Normal saline solution is administered to prevent intravascular depletion. In appreciation of the role of brain tissue shifts, hypertonic saline administration or surgical evacuation of life-threatening supratentorial infarctions by means of hemicraniectomy and duroplasty may have to be considered (see "Surgical Therapy").

b. **Hemorrhagic transformation** occurs in approximately 40% of all ischemic infarcts, and of these, 10% show secondary clinical deterioration. Hemorrhagic transformation often occurs in the first few weeks following stroke, most often in the first 2 weeks. Risk factors for hemorrhagic transformation include large strokes with mass effect, enhancement on contrast CT scans, and severe initial neurologic deficits.

c. **Seizures** occur in 4% to 6% of cases of ischemic infarction, mostly in carotid territory cortical infarcts. Infarcts in the posterior circulation are infrequently associated with seizures. Cardioembolic strokes have been found to be more epileptogenic than atherothrombotic strokes, but several studies have found no significant difference. Seizures associated with lacunar infarcts are extremely rare. Partial seizures are more common than are generalized tonic–clonic seizures. Many seizures occur within 48 hours of onset of symptoms. In general, seizures are self-limited and

TABLE 36.4 Causes of "Stroke in Evolution"

Thrombosis of a stenotic artery
Thrombus propagation
Recurrent embolism
Collateral failure
Hypoperfusion resulting from hypovolemia, decreased systemic pressure, or decreased cardiac output
Hypoxia
Brain edema
Seizures
Metabolic evolution of ischemic insult
Pneumonia
Urosepsis
Electrolyte abnormalities
Medication effects
Herniation syndromes
Brainstem compression
Hydrocephalus
Hemorrhagic transformation

respond well to antiepileptic drugs. Patients with seizures that occur in the first few days after the ischemic event do not have increased mortality. Status epilepticus is unusual.

3. **Rehabilitation.** Prevention of complications is the first stage of rehabilitation. Patients who need inpatient rehabilitation are transferred to the appropriate rehabilitation facility. The long-term prognosis for stroke depends on severity and type of neurologic deficit, the cause of the stroke, medical comorbidity, premorbid personality, family constellation, home environment, type of community and available services, and the rehabilitation team. Approximately, 50% to 85% of long-term survivors of stroke are able to walk independently, most of the recovery taking place in the first 3 months. Approximately, two-thirds of long-term survivors eventually become independent for activities of daily living, and approximately 85% of surviving patients eventually return home.

B. Specific measures.

1. **Medical therapy.** General measures and use of antithrombotic agents (antiplatelet agents or anticoagulants) and thrombolytic agents remain the mainstays of medical therapy for acute ischemic stroke.
   a. **Antiplatelet agents.** Antiplatelet agents such as aspirin, the combination of extended release dipyridamole plus aspirin, and clopidogrel play a critical role in the secondary prevention of atherothrombotic events. Antiplatelet therapy is highly effective in reducing the risk of recurrent vascular events and is recommended over warfarin for noncardioembolic ischemic strokes. Antiplatelet therapy should be avoided in the first 24 hours following the administration of intravenous tissue plasminogen activator (tPA) for acute ischemic stroke.
      (1) **Aspirin.** The mechanism of action of aspirin is irreversible inhibition of platelet function through inactivation of cyclooxygenase. Aspirin reduces the combined risk of stroke, MI, and vascular death by approximately 25%. Early (within the first 48 hours) aspirin therapy (160 to 325 mg per day) is recommended in patients with ischemic stroke who are not receiving thrombolytic therapy. The U.S. Food and Drug Administration (FDA) recommends a dose of 50 to 325 mg per day of aspirin in the secondary prevention of noncardioembolic ischemic stroke. The main side effect is gastric discomfort. A subpopulation of patients may be resistant to the antiplatelet effects of aspirin.
      (2) **Dipyridamole plus aspirin.** Dipyridamole is a cyclic nucleotide phosphodiesterase inhibitor. The Second European Stroke Prevention Study (ESPS-2) randomized 6,602 patients with previous TIA or stroke to treatment with aspirin alone (25 mg twice per day), modified-release dipyridamole (200 mg twice per day), the two agents in combination, or placebo. The investigators reported an additive effect of dipyridamole (37%) when coprescribed with aspirin. There was a decrease in stroke rate with combined treatment versus either agent alone (aspirin, 18%; dipyridamole, 16%). Both low-dose aspirin and high-dose dipyridamole in a modified release form alone were better than placebo. The combination of aspirin and dipyridamole was effective in reducing the rate of nonfatal stroke, but had little effect on the rate of MI or fatal stroke. Addition of the European and Australian Stroke Prevention Reversible Ischemia Trial data to the meta-analysis of previous trials results in an overall risk ratio for the composite of vascular death, stroke, or MI of 0.82 (95% CI 0.74 to 0.91) in favor of the dipyridamole plus aspirin regimen. A randomized clinical trial comparing aspiring plus extended release dipyridamole versus clopidogrel in more than 20,000 patients found no difference in recurrent stroke or a composite outcome of stroke, MI, or death after 2.5 years of follow-up. The main side effects of dipyridamole are gastrointestinal distress and headaches.
      (3) **Clopidogrel.** Clopidogrel is a platelet adenosine diphosphate receptor antagonist. In a study enrolling more than 19,000 patients with atherosclerotic vascular disease manifested as either recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease, 75 mg of clopidogrel was modestly more effective (8.7% relative risk reduction) than 325 mg of aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death. The side effect profile was thought

to be relatively benign, with no increased incidence of neutropenia, although a report associated the use of clopidogrel with TTP in 11 patients. Several of these patients were taking concomitant medications. Clopidogrel is a reasonable alternative in patients allergic to aspirin. The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended in patients with ischemic stroke or TIA. Functional variants in the cytochrome P450 genes can alter the effectiveness of clopidogrel.

(4) **Other agents.** Cilostazol, a phosphodiesterase III inhibitor, is often used for stroke prevention in Japan and other East Asian countries. Triflusal, that is chemically related to aspirin, is considered to be an acceptable first-line antiplatelet agent in some European countries.

(5) **Summary.** Aspirin at doses of 50 to 325 mg per day extended-release dipyridamole 200 mg plus aspirin 25 mg twice daily, or clopidogrel 75 mg per day, are all acceptable alternatives for initial therapy.

b. **Anticoagulants**

(1) ***Prevention.*** Warfarin inhibits the **vitamin K-dependent gamma-carboxylation** of factors II, VII, IX, and X. Warfarin is indicated for primary and secondary prevention of stroke among patients with nonvalvular atrial fibrillation. Data from a series of atrial fibrillation trials demonstrate an approximate two-thirds risk reduction in the rate of stroke occurrence when patients are treated to a goal international normalized ratio (INR) range of 2.0 to 3.0. The risk of stroke is the same for patients with chronic or paroxysmal atrial fibrillation. Warfarin is also indicated for prevention of stroke in patients with rheumatic atrial fibrillation, mechanical prosthetic heart valves, or other selected subgroup of patients with other high-risk cardiac sources of embolism. Dabigatran, a reversible oral thrombin inhibitor, is used as an alternative for adjusted-dose warfarin in the prevention of stroke in patients with atrial fibrillation.

(2) ***Treatment.***

(a) **Thrombolytics.** Thrombolytic therapy has been a major milestone in the management of acute ischemic stroke. In June 1996, the U.S. FDA approved the use of intravenous tPA (Alteplase) for ischemic stroke within 3 hours of symptom onset. Intravenous tPA initiated within 3 hours of symptom presentation is a first-line treatment for acute ischemic stroke in selected patients (Table 36.5). Patients are given 0.9 mg/kg/dose (maximum 90 mg dose); 10% of the total dose is administered as a loading dose over 1 minute with the remainder administered over 60 minutes. In the NINDS rt-PA Stroke Trial, favorable outcome was achieved in 31% to 50% compared with 20% to 38% of patients given placebo. Overall, for every 100 patients with acute ischemic stroke treated with intravenous tPA in the 0- to 3-hour window, 32 patients benefit and 3 patients are harmed. The major risk of treatment is symptomatic intracerebral hemorrhage that occurred in 6.4% of patients treated with intravenous tPA compared to 0.6% of patients given placebo in the NINDS rt-PA Stroke Trial.

Data by the investigators of the ECASS 3 trial show that intravenous thrombolytic therapy is also beneficial when initiated within 3 to 4.5 hours of onset of acute ischemic stroke. The ECASS 3 study had strict exclusion criteria such as age over 80 years, combination of previous stroke and diabetes mellitus, oral anticoagulant therapy (regardless of INR values), an NIHSS score of >25, and evidence of major infarct on CT scan with compromise of >one third of the MCA territory.

Certain patients, deemed unsuitable for intravenous thrombolytic therapy, may be candidates for other reperfusion strategies, including intra-arterial thrombolysis and mechanical endovascular devices.

(b) **Anticoagulants.** Randomized trials of UFH, low-molecular weight heparin, or heparinoids for the treatment of acute arterial ischemic stroke showed no proven benefits in the reduction of stroke-related mortality, stroke-related morbidity, early stroke recurrence or stroke prognosis, except in cases of cerebral venous thrombosis.

TABLE 36.5 Exclusion Criteria for Intravenous Thrombolytic Therapy within 3 Hr of Ischemic Stroke Onset

Minor or rapidly improving neurologic deficits (relative contraindication)
Seizure at the onset of symptoms (if residual impairments are postictal)
Symptoms suggestive of subarachnoid hemorrhage
Systolic blood pressure ≥185 mm Hg or diastolic blood pressure ≥110 mm Hg after two attempts to reduce blood pressure
Stroke or serious head trauma in the previous 3 mo
Major surgery in the previous 14 d
History of intracranial hemorrhage
Gastrointestinal or genitourinary bleeding in the last 21 d
Arterial puncture at a noncompressible site in the previous 7 d
Received heparin therapy within the preceding 48 hr and the aPTT is elevated
INR >1.7 or PT >15 s
Platelet count < 100,000/μl
Glucose level <50 mg/dl (<2.7 mmol/L)
MI in the previous 3 mo

2. **Surgical therapy.**
   a. **Carotid endarterectomy (CEA).** Approximately, 15% of ischemic strokes are caused by extracranial ICA stenosis. In addition to the degree of carotid artery stenosis, **plaque structure** has been postulated as a critical factor in defining stroke risk. Various features of **plaque morphology** have been used to identify symptomatic risk. **Inflammation** is also important in carotid artery plaques. Clinicopathologic correlates of examined surgical carotid plaque specimens show that **ulceration** is more prevalent among symptomatic patients, and that thrombus formation is more common in cases with ulcerated plaques. Precise determination of vessel **stenosis** has significant potential in the routine clinical assessment of ischemic cerebrovascular disease. Results from landmark prospective studies comparing best medical therapy with **CEA** provide compelling evidence of the benefit of CEA performed by experienced surgeons in improving the chance of stroke-free survival in high-risk **symptomatic patients.** Timely surgical intervention in selected patients with hemispheric TIAs, amaurosis fugax, or completed nondisabling ICA territory ischemic strokes within the previous 6 months, and with 70% to 99% diameter reducing ICA stenosis, can significantly reduce the risk for recurrent cerebral ischemia or death. With low-surgical risk, CEA also provides modest benefit in symptomatic patients with ICA stenosis of 50% to 69%, especially among men with hemispheric ischemia who are not diabetic. The procedure's benefit is greatest if done within the first 2 weeks from the ischemic event. There is no evidence that CEA provides any benefit over medical therapy if the degree of stenosis is <50%.

      Controversy still surrounds the selection of **asymptomatic patients** (60% to 99% stenosis) for CEA. Based on combined data from the Asymptomatic Carotid Atherosclerosis Study and the Asymptomatic Carotid Surgery Trial Collaborators, the 5-year risk of stroke in these patients randomized to best medical therapy was around 12%, falling to approximately 6% with CEA. This modest benefit favoring CEA assumes that operative complications are below 3%.
   b. **Carotid angioplasty and stenting (CAS).** Preliminary data of CAS suggest that CAS may have comparable efficacy to CEA. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) showed no significant difference in the composite of any stroke, MI, or death between symptomatic and asymptomatic patients receiving carotid artery stenting or CEA. In contrast to CREST, other studies have reported an excess risk of new ischemic lesions in patients who underwent CAS. Thus, the relative merit of CEA versus CAS remains a matter of intense debate.
   c. **Extracranial–intracranial (EC/IC) bypass surgery.** An early randomized study of medical therapy versus EC/IC bypass surgery failed to show a benefit for surgery.

The measurement of oxygen extraction fraction (OEF) by positron emission tomography (PET) has allowed investigators to identify particular high-risk patients who might benefit from EC/IC bypass. However, preliminary data showed no benefit in the reduction of ipsilateral ischemic stroke in patients with symptomatic ICA occlusion and increased OEF on PET.

d. **Decompressive surgery.** In some circumstances of malignant cerebral edema (malignant MCA infarction), early (<48 hours) decompressive surgery with hemicraniectomy and durotomy may be lifesaving (Fig. 36.5A–F). In cases of cerebellar infarction with mass effect, when fourth ventricular compression and hydrocephalus are the primary concerns, some neurosurgeons prefer to perform a ventriculostomy. This procedure may be associated with a risk of upward cerebellar herniation through the free edge of the tentorial incisura (Fig. 36.6). For this reason, other neurosurgeons favor posterior fossa decompressive surgery for such patients.

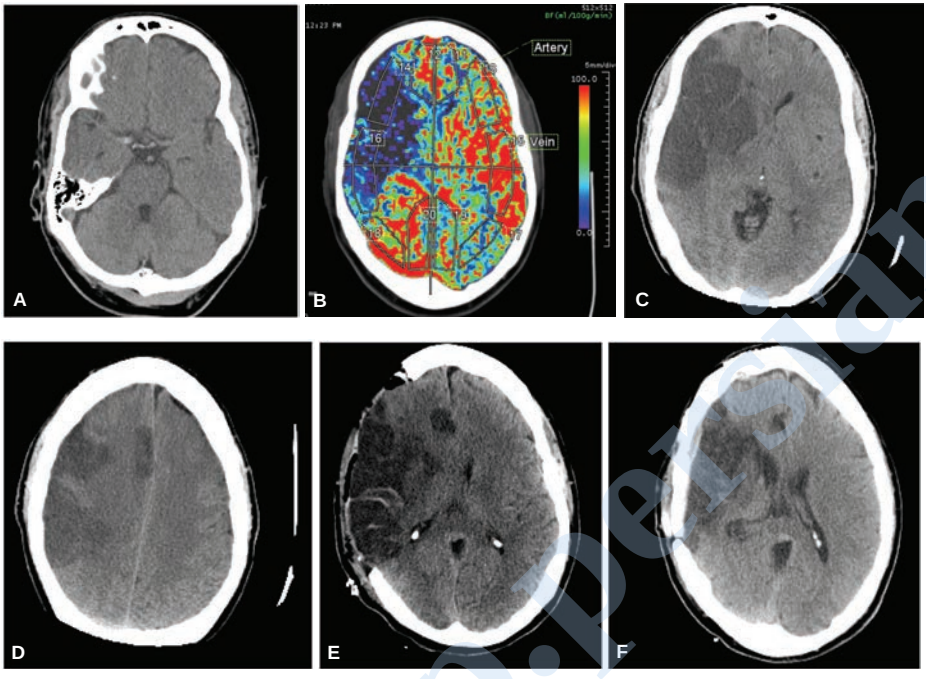

FIGURE 36.5 **A:** Noncontrast CT of the brain shows hyperdensity in the expected location of the right MCA suggestive of thrombus. There was also lost of the normal gray–white differentiation involving the right frontal and temporal lobes in the territory of the MCA. **B:** CT perfusion demonstrates decreased CBF. There was also decreased cerebral blood volume with associated increased mean transit time (not shown in this composite) in the right frontal and temporal lobes compatible with infarct. **C:** Large area of ischemic change involving the distribution of the right MCA. There is mass effect with midline shift to the left approximately 1.1 cm. There is no evidence of hemorrhagic transformation. **D:** Large area of ischemic change involving the distribution of the right MCA as well as a smaller focus involving the distal right ACA territory. **E:** Postoperative changes from a large right hemicraniectomy and duraplasty. A previously noted subfalcine herniation to the left has decreased from 8 to 4 mm. **F:** Postsurgical change of recent large right convexity cranioplasty. There is abnormal low density and focal volume loss involving the cortex and subcortical white matter of the right cerebral hemisphere, predominately in the right MCA distribution including the right basil ganglia as well as portions of the right ACA territory. These findings are consistent with encephalomalacia at the sites of chronic infarct. There is ex vacuo dilatation of the frontal horn of the right lateral ventricle. CBV, cerebral blood volume; MTT, mean transit time.

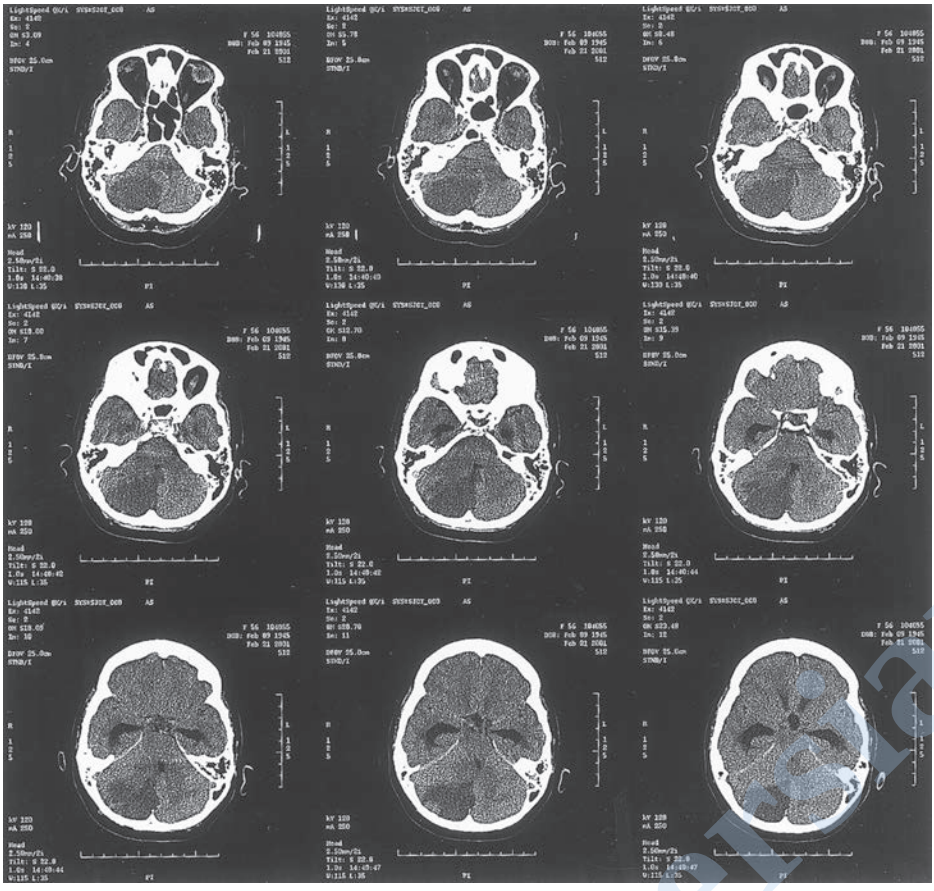

FIGURE 36.6 Axial unenhanced CT demonstrates a large area of low attenuation involving the inferior and posterior aspects of the right cerebellar hemisphere (territory of the posterior–inferior cerebellar artery) causing effacement of the brainstem cisterns and compression of the fourth ventricle, causing acute obstructive hydrocephalus. The patient required a right occipital craniectomy secondary to her large edematous cerebellar infarction.

Recommended Readings

Adams HP Jr, Adams RJ, Del Zoppo G, et al. Guidelines for the early management of patients with ischemic stroke. Guidelines Update. *Stroke*. 2005;36:916–923.

Amarenco P, Bogousslavsky J, Callahan A, et al. High dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559.

Asymptomatic Carotid Surgery Trial Collaborators. The MRC Asymptomatic Carotid Surgery Trial (ACST): carotid endarterectomy prevents disabling and fatal carotid territory strokes. *Lancet*. 2004;363:1491–1502.

Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet*. 2005;366:1267–1278.

Bhogal SK, Teasell R, Folley N, et al. Lesion location and post-stroke depression: systematic review of the methodological limitations in the literature. *Stroke*. 2004;35:794–802.

Brott TG, Hobson RW 2nd, Howard G, et al.; CREST Investigators. Stending versus endarterectomy for treatment of carotid artery stenosis. *N Engl J Med*. 2010;363:11–23.

CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.

Donnan GA, Fisher M, Macleod M, et al. Stroke. *Lancet*. 2008;371:1612–1623.
European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) stenosis. *Lancet*. 1991;337:1235–1243.
European Stroke Prevention Study (ESPS-2) Working Group. ASA/dipyridamole is superior to either agent alone and to placebo. *Stroke*. 1996;27:195.
Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273:1421–1428.
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary of the third report of the National Cholesterol Education Program (NCEP). *JAMA*. 2001;285:2486–2497.
Grubb RL Jr, Powers WJ, Derdeyn CP, et al. The Carotid Occlusion Surgery Study. *Neurosurg Focus*. 2003;14:1–7.
Hacke W, Kaste M, Bluhmki E, et al.; ECASS Investigators. Thrombolysis with Alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.
Halkes PH, van Gijn J, Kappelle LJ, et al. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet*. 2006;367:1665–1673.
Hankey GJ, Counsell C, Sandercock P. Low molecular weight heparins or heparinoids versus standard unfractionated heparin for acute ischemic stroke (Cochrane review). In: *The Cochrane Library*. Oxford: Systemic Reviews; 2005(3). Update Software.
Hart RG, Halperin JL, Pearce LA, et al. Lessons from The Stroke Prevention in Atrial Fibrillation trials. *Ann Intern Med*. 2003;138:831–838.
International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet*. 1997;349: 1569–1581.
Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischemic attack. *Lancet*. 2007;369:283–292.
Kase CS, Albers GW, Bladin C, et al. Neurological outcome in patients with ischemic stroke receiving enoxaparin or heparin for venous thromboembolism prophylaxis. Sub-analysis of the prevention of VTE after acute ischemic stroke with LMWH (PREVAIL) study. *Stroke*. 2009;40:3532–3540.
Lawes CM, Bennett DA, Feigin VL, et al. Blood pressure and stroke: an overview of published studies. *Stroke*. 2004;35:776–781.
Meier P, Knapp G, Tamhane U, et al. Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomized controlled clinical trials. *BMJ*. 2010;340:c467.
Mohr JP, Thompson JLP, Lazar RM, et al. Comparison of warfarin and aspirin in the prevention of recurrent ischemic stroke. *N Engl J Med*. 2001;345:1444–1451.
National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
NINDS. *Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke*. Bethesda, MD: NINDS; 1997. NIH publication 97-4239.
North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445–453.
Publication Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. *JAMA*. 1998;279:1265–1272.
Rothwell PM, Eliasziw M, Gutnikov WCP, et al.; for the Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915–924.
Sacco RL, Adams R, Alpas G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association, American Stroke Association, Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention. *Stroke*. 2006;37:577–617.
Staessen JA, Gasowski J, Wang JF, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet*. 2000;355:865–872.
Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the cerebral artery: a pooled analysis of three randomized controlled trials. *Lancet Neurol*. 2007;6:215–222.
Warlow C, Sudlow C, Dennis M, et al. Stroke. *Lancet*. 2003;362:1211–1224.

CHAPTER

37 Hemorrhagic Cerebrovascular Disease

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Hemorrhagic cerebrovascular disease includes nontraumatic bleeding that occurs primarily in the brain (intracerebral hemorrhage [ICH]), the ventricles (intraventricular hemorrhage [IVH]), the subarachnoid space (subarachnoid hemorrhage [SAH]), or the subdural space (subdural hematoma [SDH]). Bleeding often simultaneously involves the brain, the ventricles, and the subarachnoid space.

Nontraumatic intracranial hemorrhage (hemorrhagic stroke/cerebral hemorrhage) annually occurs in approximately 75,000 Americans. The 1-month mortality of intracranial hemorrhage is approximately 35% to 50%; most of the deaths happen within the first 24 to 48 hours of the illness. Approximately 10% of patients do not survive long enough to reach a hospital or they die shortly after arriving in an emergency department. Mortality is highest among persons older than 60, those with secondary intraventricular bleeding, and those with severe neurologic impairments (in particular, coma). Only 20% of survivors of intracranial hemorrhages achieve functional independence.

Although the incidence of stroke, including hypertensive hemorrhage, has declined, the rate of SAH, largely due to ruptured intracranial aneurysms, remains stable. The frequency of hemorrhagic stroke may increase in the future as the result of the aging of the American population, an increase in the prevalence of cerebral amyloid angiopathy, increased abuse of drugs that cause hypertensive crises, and the widespread prescription of medications that affect coagulation. Although the chances of hemorrhagic stroke increases with advancing age, intracranial bleeding also occurs in children and young adults. Because ischemic strokes are relatively uncommon among children, adolescents, and persons younger than 45, the relative proportion of hemorrhagic strokes is very prominent in these age groups. The patient's age also affects the diagnosis of the cause of intracranial hemorrhage. For example, cerebral amyloid angiopathy and hypertension are important causes of bleeding among the elderly, whereas the average age of patient with a ruptured CNS vascular malformation is approximately 30 years. Even when trauma is excluded, hemorrhagic stroke is more frequent among men than among women. The incidence of hemorrhagic stroke is higher among Americans of African or Asian heritage than among those with European ancestry. Intracranial hemorrhage is an especially important cause of death among young African Americans.

I. CAUSES OF HEMORRHAGIC STROKE

Intracranial hemorrhages are secondary to a large variety of diseases (Table 37.1). In most cases, the most likely cause of bleeding can be identified.

A. Occult craniocerebral trauma. Trauma is a potential cause of intracranial bleeding—typical SDH or epidural hematomas or parenchymal contusions. A history of injury may be lacking when a patient is found unconscious and other clues must be sought, such as lacerations or soft-tissue swelling. Conversely, a patient with a primary hemorrhage may suffer secondary trauma.

B. Arterial hypertension. Either acute or chronic arterial hypertension may be a cause of ICH. Chronic hypertension leads to degenerative changes in small penetrating arteries in the deep structures of the brain. Sudden, severe hypertension may overwhelm the autoregulatory responses of the cerebral vasculature and an arteriole may rupture. Acute and severe arterial hypertension may be secondary to acute glomerulonephritis, eclampsia, severe emotional stress, or the use of a sympathomimetic agent. The most common sites for hypertensive ICH are the basal ganglia (putamen), thalamus, brainstem, cerebellum, or lobar white matter. Hypertension should be considered as the likely cause

TABLE 37.1 Causes of Hemorrhagic Stroke

Occult craniocerebral trauma
Aneurysms
Saccular (berry) aneurysm
Nonsaccular aneurysm
Infective
Neoplastic
Traumatic
Dolichoectatic
Dissection
Vascular malformations
AVM
Cavernous malformation
Developmental venous anomaly
Telangiectasia
Arterial hypertension
Chronic hypertension (Charcot–Bouchard's aneurysm)
Acute hypertension
Eclampsia
Stress-related
Postoperative hyperperfusion syndrome
Moyamoya disease/syndrome
Drug abuse
Amphetamine/methamphetamine
Cocaine
Tumors
Primary
Metastatic
Cerebral amyloid angiopathy
Vasculitis
Multisystem necrotizing vasculitis
Isolated CNS vasculitis
Bleeding disorders
Hemophilia
Sickle cell disease
Thrombocytopenia
Leukemia
Thrombolytic agents
Antithrombotic agents
Venous thrombosis
Hemorrhagic transformation of ischemic stroke

of a hematoma located in deep gray matter structures of the cerebral hemisphere if a patient has a history of hypertension. Other features of chronic hypertension, such as retinopathy, renal dysfunction, or left ventricular hypertrophy, support the diagnosis. Even though hemorrhagic stroke often is attributed to hypertension because of the presence of an elevated blood pressure measured upon arrival to an emergency department, arterial hypertension is common among acutely ill patients with intracranial hemorrhage, and the finding should not automatically lead to the diagnosis of hypertensive hemorrhage.

C. Saccular aneurysm. Rupture of a saccular aneurysm is the most common cause of nontraumatic SAH and it is an important cause of ICH. Approximately 1% to 5% of adults harbor intracranial aneurysms, but a minority of these lesions actually rupture. In general, the risk of rupture is correlated with the size of the aneurysm, with the highest risk found with aneurysms larger than 6 to 8 mm in diameter. Patients with autosomal dominant polycystic kidney disease have a high prevalence of intracranial

aneurysms. Approximately 10% of patients have a family history of cerebral aneurysms. Approximately 85% of saccular aneurysms are in the carotid circulation with the most common sites being the junction of the internal carotid artery—posterior communicating artery, the bifurcation of the middle cerebral artery, and the anterior communicating artery. The most common locations in the posterior circulation are the bifurcation of the basilar artery and the origin of the posterior inferior cerebellar artery.

D. Other aneurysms. Infective, neoplastic, and traumatic aneurysms are rare causes of intracranial hemorrhage. These lesions usually are located in peripheral branch pial arteries on the cortical surface of the cerebral hemispheres. They usually are smaller than saccular aneurysms, but they have a relatively high risk of hemorrhage. Dolichoectatic (fusiform) aneurysms are tortuous, elongated arterial enlargements most commonly found in the basilar arteries of patients with extensive atherosclerosis or young men with Fabry's disease. Hemorrhage is an uncommon complication. Spontaneous or traumatic dissecting aneurysms of intracranial arteries, particularly of the basilar or distal vertebral arteries, are potential causes of atypical SAH.

E. Vascular malformations. Vascular malformations are classified as arteriovenous malformation (AVM), developmental venous anomaly, cavernous malformation, and telangiectasias. They may be located in any part of the brain. Although familial cases, as with hereditary hemorrhagic telangiectasia or familial cavernous malformations, may occur, most are sporadic. The prevalence of vascular malformations is less than that of saccular aneurysms, and most affected persons never have hemorrhage. ICH is the presenting symptoms in approximately 50% of cases. Non-hemorrhagic symptoms include seizures, recurrent and stereotypic headache, or progressive neurologic impairments. Patients with large AVM leading to turbulent blood flow may have pulsatile tinnitus and a cranial bruit may be auscultated.

F. Cerebral amyloid angiopathy. It (congophilic angiopathy) is a leading cause of lobar ICH in the elderly. With aging, amyloid is deposited in the walls of cortical and leptomeningeal arterioles. Presumably, the protein accumulation leads to vascular fragility and bleeding. The hemorrhages, which are most commonly located in the frontal and parietal lobes, usually arise at the junction of the white matter and cerebral cortex. Multiple or recurrent hemorrhages are common. Cerebellar hemorrhages may also develop. Amyloid angiopathy should be considered as the likely cause of lobar ICH among persons older than 75. Because approximately 70% of affected patients also have a history of Alzheimer's disease, a past history of dementia or cognitive decline increases the likelihood that an ICH in an elderly patient is due to amyloid angiopathy.

G. Vasculitis. Multisystem or isolated CNS vasculitis is a rare cause of intracranial hemorrhage. Bleeding is most often associated with a necrotizing vasculitis, such as polyarteritis nodosa. Vasculitis may be the cause of bleeding among some young patients who have hemorrhagic stroke after the use of a sympathomimetic drug.

H. Bleeding disorders. Intracranial hemorrhage may complicate several inherited or acquired bleeding diatheses, including hemophilia, sickle cell disease, thrombocytopenia, or leukemia. It may also complicate the use of thrombolytic or antithrombotic agents. In general, the severity of bleeding is worse, and the prognosis is poorer among patients with bleeding secondary to a coagulation disorder than among persons with spontaneous hemorrhages. Intracranial bleeding is a side effect of treatment for oral anticoagulants or thrombin inhibitors, and this complication should be considered whenever a patient has acute neurologic symptoms while taking oral anticoagulants even if there is no other evidence of bleeding. The risk of ICH is especially high among the elderly and persons who have leukoaraiosis present on brain imaging studies. Persons with a past history of stroke or poorly controlled hypertension also have a high risk of bleeding secondary to oral anticoagulants. The risk of intracranial bleeding increases when the international normalized ratio (INR) exceeds 3 to 4. The frequency of hemorrhagic stroke is lower with antiplatelet agents than with oral anticoagulants. The combination of aspirin and clopidogrel is more likely to be associated with bleeding than the use of either medication alone especially among persons with a history of stroke. The combination of warfarin and aspirin has a higher risk of bleeding than the administration of either agent alone.

I. **Drug abuse.** Intracranial hemorrhage has been attributed to the abuse of medications such as cocaine or methamphetamine. These agents may lead to bleeding because of sudden increases in blood pressure or because of the development of a vasculitis. Intracranial hemorrhage has also been associated with heavy alcohol use.

J. **Moyamoya disease** is an uncommon cause of hemorrhagic stroke among young adults and children. The arteriographic hallmark of moyamoya is occlusions of the major arteries of the anterior circulation and the appearance of a mesh of fine blood vessels at the base of the brain. Moyamoya disease is inherited on an autosomal dominant basis and is most common among persons of northeastern Asia. It is also diagnosed when the arteriographic findings occur among patients with a number of acquired disorders. Hemorrhages may be secondary to rupture of an aneurysm (most commonly in the posterior circulation) or rupture of small collateral channels.

K. **Venous thrombosis.** Occlusion of a cortical vein (cortical venous thrombosis) or sinus (sinus thrombosis) is an uncommon etiology of hemorrhagic stroke. Bleeding is most common among patients with thrombosis of the superior sagittal sinus; in this situation, the areas of hemorrhage are parasagittal in location bilaterally and in a thumbprint pattern. The clinical course of venous thrombosis differs from that of most other hemorrhagic strokes. Most patients have worsening headaches, seizures, altered consciousness, and focal neurologic signs that evolve over a few days. Venous thrombosis often develops in the peripartum period, but it also occurs among persons who are dehydrated, have malignant disease, have undergone a recent cranial operation, or have an otolaryngologic infection.

L. **Brain tumors.** Hemorrhage may be the initial symptom of a highly vascular primary or metastatic brain tumor, including choriocarcinoma, melanoma, or carcinoma of the kidney, thyroid, liver, lung, or breast. The most common primary tumors are glioblastoma or pilocytic astrocytoma. Patients may have a history of evolving neurologic symptoms such as headache or personality changes before the bleeding event. The presence of extensive brain edema in the first hours after hemorrhages or multiple hemorrhagic lesions should prompt consideration of an underlying brain tumor.

M. **Hemorrhagic transformation of an ischemic stroke.** Modern brain imaging allows discovery of asymptomatic hemorrhagic changes in the ischemic lesion in a sizable proportion of patients with a recent stroke. A smaller percentage of patients have neurologic worsening secondary to hemorrhagic transformation of the infarction. The risk of this complication is increased with the use of a thrombolytic within the first hours after stroke.

II. MANIFESTATIONS OF HEMORRHAGIC STROKE

The clinical features of hemorrhagic stroke are similar in both adults and children. The symptoms and signs of IVH and SAH may differ from those of ICH in that focal neurologic impairments usually are absent or subtle. Because of the absence of focal neurologic signs, errors in diagnosis are more likely to occur among patients with SAH than among patients with bleeding primarily in the brain.

A. History.

1. Hemorrhagic stroke usually is a sudden, dramatic event. The patient or observers often relate the circumstances surrounding the onset of symptoms. A headache, of any quality and location, usually is described as intense and often is described as the "worst headache of my life." A headache accompanied by a transient loss of consciousness or one that is of cataclysmic onset is a premier symptom of SAH. Approximately 40% of patients with ICH will complain of severe headache. Other symptoms include nausea, vomiting, prostration, photophobia, phonophobia, and nuchal rigidity. The presence of nausea and vomiting and focal signs suggestive of a stroke in a cerebral hemisphere is predictive of a hemorrhagic event.
2. Disturbances in consciousness are common. Prolonged unresponsiveness (coma) occurs among patients with major hemorrhages. Transient alteration in alertness at the time of bleeding (syncope) may also happen. Disorientation, confusion, or delirium may also

occur. Although focal or generalized seizures may develop, recurrent seizures or status epilepticus are uncommon.

3. Focal neurologic signs reflect the location of the hematoma. The most common pattern is a contralateral hemiparesis and hemisensory loss secondary to a hematoma in the basal ganglia. Patients with cerebellar hemorrhage often have a subacute course. They report headache, dizziness (vertigo), disturbed balance, nausea, and vomiting. Signs of increased intracranial pressure (ICP) or brainstem compression subsequently appear, including cranial nerve palsy, motor impairment, and disturbed consciousness. Although most patients with SAH or primary IVH do not have focal neurologic signs, some patients with aneurysms will have focal findings. The most common is a third nerve palsy secondary to a ruptured posterior communicating artery aneurysm.

B. Examination.

1. **General examination.** Assessment of the vital signs and the airway, breathing, and circulation (ABCs) of emergency care are the first steps of the examination (Table 37.2). Vital signs are measured frequently, and close neurologic monitoring is required. The airway should be secured for patients with impaired consciousness, seizures, vomiting, or bulbar dysfunction. Patients with severe hemorrhage often have respiratory abnormalities that lead to hypoxia, hypercapnia, or acidosis. Fever is relatively common, and it is especially prominent among patients with IVH. Electrocardiographic abnormalities and cardiac arrhythmias may also be detected. Most patients have elevated blood pressures.

   Detection of a bruit over the head or neck suggests an AVM. Multiple areas of ecchymosis or petechiae point to infective endocarditis, recent trauma, or an underlying coagulation disorder. Evidence of cervical spine, facial or cranial injury, such as a Battle's sign (basilar skull fracture) should be sought. Neck pain or tenderness may

TABLE 37.2 Examination of a Patient with Suspected Intracranial Hemorrhage

Vital signs
Airway
Breathing and respiratory pattern
Heart rate and rhythm
Temperature
Blood pressure
Cardiovascular examination
Screening for bleeding elsewhere
Petechiae
Ecchymosis
Signs of craniocerebral trauma
Battle sign
Raccoon eyes
Ocular hemorrhage
Scalp laceration
Signs of meningeal irritation
Brudzinski sign
Kernig sign
Ocular signs
Subhyaloid, retinal or conjunctival hemorrhage
Papilledema
Level of consciousness
Glasgow Coma Scale
Other neurologic signs
Cognition and language
Articulation
Motor
Sensory
Cranial nerves
Cerebellar

represent an associated spine fracture in a patient with craniocerebral trauma and hemorrhage. The neck should not be flexed to check for signs of meningeal irritation until the possibility of cervical spine fracture is excluded.

Meningeal irritation is caused by blood in the subarachnoid space. Nuchal rigidity (Brudzinski's sign) may not be present in patients with a hematoma restricted to the parenchyma or in comatose patients. A stiff neck is prominent among most patients with SAH, but this sign may take several hours to appear. Ocular hemorrhages (subhyaloid, conjunctival, or retinal) may be detected in approximately 20% of patients; their presence is highly specific for serious hemorrhages. Because the course of the illness usually is short, papilledema is not commonly observed in the first hours of the illness.

2. **Assessment of consciousness** is the most important component of the neurologic examination because the level of consciousness correlates strongly with the severity of the hemorrhage and prognosis. Although the easily calculated Glasgow Coma Scale score was originally developed to assess patients with head injuries, it is directly applicable to persons with nontraumatic brain hemorrhages. In general, a score of eight or less on the Glasgow Coma Scale correlates with a very poor prognosis.
3. **The rest of the neurologic examination** is aimed at detecting abnormalities that reflect the location of a hemorrhage within the brain. Depending upon the location of the hemorrhage, motor, sensory, language, or cranial nerve impairments are found.

III. DIFFERENTIAL DIAGNOSIS OF HEMORRHAGIC STROKE

The differential diagnosis is not extensive. The brief duration, clinical severity, and prominent focal neurologic signs are relatively specific.

A. **Ischemic stroke.** The leading alternative diagnosis is acute ischemic stroke. Although there are no unique features, patients with hemorrhagic stroke generally are more seriously ill than those with ischemic stroke. The symptoms usually are more severe than those that can follow occlusion of a single artery, as in ischemic stroke. Headaches, early depression in consciousness, nausea, vomiting, photophobia, and phonophobia are also more prominent in hemorrhagic stroke.

B. **Craniocerebral trauma.** Differentiation of trauma from spontaneous bleeding can be difficult when a patient is comatose and no history is available. In general, hemorrhages deep in the brain are not the result of trauma. Conversely, multiple small cortical petechial hemorrhages in the frontal, temporal, and occipital poles usually are secondary to injuries.

C. **SAH.** In contradistinction to that of ICH, the differential diagnosis of SAH is broad (Table 37.3). Although patients with SAH usually seek medical attention because of the severity of their symptoms, physicians may be misled. The diagnosis of SAH is missed in approximately 15% of cases, most commonly among the least seriously ill patients. Failure to recognize a ruptured aneurysm has serious implications because of the risk of a potentially fatal recurrent hemorrhage and because of the availability of effective therapies that can be administered early. The only way to avoid missing an SAH is to maintain a high index of suspicion. Patients who have the sudden onset of an exceptionally severe headache or a headache associated with loss of consciousness should be evaluated for SAH. The absence of focal neurologic signs or meningeal irritation does not preclude the diagnosis. Atypical symptoms include severe neck, face, shoulder, eye, or ear pain. A ruptured aneurysm in the posterior fossa may produce neck or back pain as a primary symptom.

TABLE 37.3 Differential Diagnosis of SAH

Migraine headache	Tension headache
Sinusitis	Viral meningitis
Influenza	Hypertensive crisis
Eclampsia	Head injury
Cervical spine injury	Cervical herniated disk
Alcohol intoxication	Drug intoxication

IV. DIAGNOSTIC STUDIES

The goals of the emergency evaluation are to confirm hemorrhage as the cause of the neurologic symptoms and to look for acute complications (Table 37.4). These critically ill persons are at high risk for a variety of serious neurologic or medical complications; the most frequent are brain edema, hydrocephalus, increased ICP, and seizures. Medical complications include myocardial ischemia, cardiac arrhythmias, gastrointestinal bleeding, respiratory abnormalities, and fluid and electrolyte disturbances. Before they are moved, obtunded patients with possible craniocerebral trauma should have imaging of the cervical spine to eliminate an occult fracture.

A. CT of the brain. This is the single most important diagnostic test because it is available at most hospitals, relatively inexpensive, noninvasive, and easy to perform. The yield of unenhanced CT is extraordinarily high. When CT is performed within 24 hours of onset, blood density can be detected in almost 100% of patients with ICH and approximately 95% of those with SAH. The presence of a "spot sign" on an early, contrast enhanced CT study/computed tomographic angiography (CTA) predicts those cases that may have enlargement of the hematoma. Sequential CT studies obtained during the first hours after the ictus often shows enlargement of a hematoma presumably as a result of continued bleeding. CT may miss a small collection of subarachnoid blood in a patient with a mild hemorrhage or if the bleeding is restricted to the posterior fossa. If CT is performed several days after the ictus, the yield of the test in detecting SAH decreases because the blood may be been reabsorbed. The location and pattern of blood also predicts the underlying pathology or the site of a ruptured aneurysm. The presence of subarachnoid blood restricted to the perimesencephalic cisterns usually is not due to an aneurysm. CT also detects early complications including brain edema and hydrocephalus. CT provided prognostic information, for example, large amounts of subarachnoid blood are predictive of vasospasm and ischemic stroke after SAH. The presence of IVH complicating either ICH or SAH also forecasts a poor prognosis.

TABLE 37.4 Diagnostic Studies of Patients with Hemorrhagic Stroke

Initial emergency studies
- CT of the brain
- Cervical spine films (if a neck injury is possible)
- ECG
- Pulse oximetry
- CBC and platelet count
- Partial thromboplastin time
- Prothrombin time (INR)
- Serum electrolytes
- Blood glucose
- CSF examination (if SAH suspected and CT is negative)

Subsequent emergency studies
- CTA
- MRI of the brain and MRA
- Arteriography

Additional studies
- Transcranial Doppler ultrasonography
- Blood cultures (if infective endocarditis suspected)
- Fibrinogen
- Sickle cell screen
- Erythrocyte sedimentation rate
- C-reactive protein
- Urine and blood screens for illicit drugs
- Brain and meningeal biopsy

Contrast-enhanced CT may detect an AVM or aneurysm. CTA is a valuable method to image the vasculature at the base of the brain and, in particular, to examine the anatomic relations of saccular aneurysms. Because CTA can show three-dimensional images of an AVM, it may be used to help planning for interventions.

B. MRI. This test depicts intracranial bleeding and provides additional data about the likely cause of hemorrhage. Multisequence MRI may be as sensitive as CT in the detection of intracranial bleeding. Although it is more expensive and not as widely available as CT, MRI does have advantages. Because of the changes in the responses of iron in the hematomas of different ages, MRI provides information about the age of the hemorrhagic lesion. A gradient echo sequence is very useful in detecting microhemorrhages, which are a hallmark of amyloid angiopathy. Abnormal flow voids can be found with vascular malformations. Magnetic resonance angiography (MRA) can also be performed to detect aneurysms or vascular malformations.

C. CSF examination. The frequency of examination of the CSF has declined with the advent of brain imaging. If CT shows a hemorrhage, there is little reason to do a lumbar puncture (LP) to search for blood. Conversely, CSF examination is important if SAH is suspected and CT does not show blood. CSF examination may help detect bleeding among alert patients who have mild signs. The risk of neurologic complications, including herniation, is low in an alert patient who does not have focal impairments and no mass found on CT. Determining whether the source of bloody CSF is an intracranial hemorrhage or a traumatic LP (bloody tap) can be difficult. Bloody CSF from SAH generally does not clear in sequentially collected tubes. Xanthochromia (yellowing) of the CSF supernatant after centrifugation is the most reliable sign, but it can take up to 12 hours after SAH to appear. A physician should immediately centrifuge a bloody CSF specimen to check for xanthochromia because a delay of several hours may give a false-positive result. The CSF findings evolve over time, and if the LP is delayed several days, only slightly yellow fluid, an elevated CSF protein level, or an inflammatory response that mimics viral meningitis may be detected.

D. Arteriography. The role of arteriography has declined with advances in the use of MRA and CTA to detect vascular malformations and aneurysms. It usually is not needed for evaluation of older patients with a history of hypertension and a hemorrhage in the basal ganglia or thalamus. It may be useful in detecting small aneurysms or vasculitis. It may also be used to detect vasospasm following SAH. A relatively common scenario for arteriography is its performance as a preliminary step for endovascular treatment for the source of bleeding or before treatment for vasospasm.

E. Other diagnostic studies. Patients should have an electrocardiography and hematologic, coagulation, and biochemistry studies as part of their evaluation. These tests are done to screen for medical complications and to search for a cause of hemorrhage.

V. TREATMENT

A. Prevention. Prevention is the most cost-effective strategy for treatment of patients at a high risk for hemorrhagic stroke. Administration of antihypertensive agents to patients with either acute or chronic sustained elevations of blood pressure may lower the risk of intracranial hemorrhage. Cautious use of thrombolytic, anticoagulant, and antiplatelet agents should also decrease the likelihood of intracranial bleeding. Management of inherited or acquired disorders of coagulation, including the administration of clotting factors, also lowers the risk of hemorrhage. Management of an unruptured AVM or aneurysm often is recommended. Choices include endovascular or direct surgical occlusion of larger aneurysms. Surgical resection, focused radiation, or endovascular therapies are potential therapies for treatment of AVM. However, recent evidence suggests that in some cases the risks of the interventions may be greater than the likelihood of hemorrhage.

B. Referral and admission. Patients with acute hemorrhagic stroke are critically ill. Inpatient care is warranted because intracranial hemorrhage is life-threatening and is accompanied by serious medical or neurologic complications. The facilities and

personnel required for successful care of these patients may not be available at most community hospitals. Admission to a specialized treatment facility that has monitoring capabilities or an ICU usually is needed. The high-risk nature of hemorrhagic stroke means that most patients should be referred to centers that have neurologic and neurosurgical expertise.

C. General management. Measures for control of acute medical and neurologic complications are part of emergency treatment (Table 37.5). Endotracheal intubation and ventilatory assistance may be needed. Hypoxic patients should receive supplemental oxygen. Fever should be treated. Access for intravenous administration of medications and fluids is needed, and normal saline solution is infused slowly. Hypotonic solutions generally are avoided because of their potential effects on the formation of edema and because many patients have hyponatremia. Hypoglycemia or hyperglycemia should be managed. Cardiac monitoring to detect serious arrhythmias and frequent measurements of vital signs and the neurologic status are performed. Symptoms such as headache, agitation, nausea, and vomiting warrant treatment. Patients who have had seizures are given anticonvulsants, but prophylactic use of anticonvulsants to patients who have not had seizures is controversial. Because of fears that stress of a seizure may cause rebleeding, many physicians prophylactically prescribe anticonvulsants to patients with ruptured aneurysms.

D. Treatment for arterial hypertension. Elevated blood pressure may worsen intracranial bleeding, promote edema formation, or induce recurrent aneurysmal rupture. It usually declines as pain, agitation, seizures, and vomiting are controlled. The level of blood pressure that mandates medical treatment is not known, but there is a consensus to treat a systolic pressure >200 mm Hg or mean arterial pressure >150 mm Hg. Because an elevated ICP promoted arterial hypertension, special caution is needed when lowering the blood pressure among patients with intracranial hypertension. In general, a goal is to lower the blood pressure by approximately 15% per day. Responses to antihypertensive agents often are exaggerated. Short-acting parenteral medications are preferred because the dosages can be titrated in response to the patient's blood pressure and neurologic status (Table 37.6). In addition, caution should be exercised when using sodium nitroprusside because its secondary cerebral vasodilatory effects may worsen increased ICP.

E. Halting continued bleeding. Recombinant factor VIIa was used to treat ICH, but a recent trial showed that it did not improve outcomes. Patients with intracranial hemorrhage secondary to a defect in coagulation should receive the appropriate antidotes including protamine, vitamin K, clotting factors, or platelets.

F. Increased ICP and brain edema. Management of increased ICP is important. Monitoring of ICP may be used to guide treatment for critically ill patients. Impaired venous return, agitation, fever, hypoxia, hypercapnia, and hypoventilation aggravate increased ICP and should be managed. Early measures include elevation of the head of the bed, modest fluid restriction, and avoidance of potentially hypo-osmolar fluids. Corticosteroids are not helpful. Intubation and hyperventilation are prescribed when a patient's condition is deteriorating. Hyperosmolar therapies, which often are prescribed with seriously elevated ICP, include 20% mannitol or hypertonic saline.

G. Emergency surgical management. An early decision involves the need for surgical evacuation of a hematoma that is causing mass effects or increased ICP. A ventricular catheter may be used to drain CSF if the patient has secondary hydrocephalus; it may

TABLE 37.5 Emergency Management of Hemorrhagic Stroke

ABC of life support
Frequent measures of vital signs and blood pressure
Frequent assessments of neurologic status
Cardiac monitoring
Control fever
Supplemental oxygen if hypoxia is present
Intravenous access with slow infusion of normal saline
Control pain, nausea, vomiting, and seizures

lower ICP and forestall the need for a craniotomy. Removal of a large hematoma may be a lifesaving procedure. Choices include an open craniotomy, minimally invasive surgery, and endoscopic aspiration. Administration of thrombolytic agents to add aspiration of the hematoma including an IVH has been attempted. The location and size of the hematoma and the patient's neurologic status, course, and general health affect such a decision (Table 37.7). In general, surgery is recommended for the treatment of a large cerebellar hematoma that is compressing the brainstem or obstructing CSF outflow. Patients with lobar hematomas within 1 cm of the cortical surface can be considered for surgery. However, patients with small-to-moderate-sized hematomas of the cerebral hemisphere usually do not need surgery. Patients with hemorrhages in the thalamus and basal ganglia usually are not treated with surgery. There is no evidence that surgical evacuation of such hematomas improve outcomes. There are no data about the utility of decompressive craniectomy to improve outcomes after intracranial hemorrhage.

H. General inpatient care. Emergency management is continued after admission to an ICU. Bed rest is maintained until the patient's status has stabilized. Careful nursing care, monitoring, and regular assessments of the patient's condition and vital signs are continued. To decrease the risk of aspiration and pneumonia, liquids and food are not given by mouth until the patient's ability to swallow safely has been confirmed. If the patient cannot take fluids by mouth, a nasogastric tube should be placed. Care in avoiding pulmonary complications is part of general management. Modest fluid restriction is continued for patients who have a large hematoma. Management of intravenous fluids should emphasize maintaining normal electrolyte levels. Some patients will have hyponatremia secondary to cerebral salt wasting, and these patients will need hypertonic fluids. Incontinence often mandates placement of an indwelling bladder catheter.

TABLE 37.6 Emergency Management of Arterial Hypertension

If systolic blood pressure >200 mm Hg or mean blood pressure >150 mm Hg
Aggressive lowering of blood pressure with intravenous infusion
Monitor blood pressure every 5 min
If systolic blood pressure >180 mm Hg or mean blood pressure >130 mm Hg and evidence of increased ICP
Reduce blood pressure with intermittent or continuous medications
Keep cerebral perfusion pressure >80 mm Hg
If systolic blood pressure >180 mm Hg or mean blood pressure >130 mm Hg and no evidence of increased ICP
Modest reduction of blood pressure
Intermittent or continuous infusion of medications
Choices of medications
Labetalol
Intermittent—5–20 mg every 15 min
Continuous—2 mg/min (maximum 300 mg in 1 d)
Nicardipine
Continuous—5–15 mg/hr
Esmolol
Intermittent—250 μg/kg push loading dose
Continuous—25–300 μg/kg/min
Enalapril
Intermittent—1.25–5 mg every 6 hr
Hydralazine
Intermittent—5–20 mg every 30 min
Continuous—1.5–5 μg/kg/min
Nitroprusside
Continuous—0.1–10 μg/kg/min
Nitroglycerine
Continuous—20–400 μg/min

TABLE 37.7 Indications for Emergency Surgical Evacuation of Hematoma

Surgery indicated
Cerebellar hematoma 0.3 cm in diameter with compression of brainstem or development of hydrocephalus
Hemorrhage with a structural lesion (aneurysm or AVM) that can be managed surgically
Moderate-to-large lobar hematoma close to the cortical surface
Surgery not indicated
Small hematoma or minimal impairment
Large, deep hematoma
Patient with very severe impairment

Because of the risk of urinary tract infection, the catheter should be removed as soon as possible. Because bedridden patients have a high risk of deep venous thrombosis that may lead to pulmonary embolism, they are treated with alternating pressure devices and antiembolism stockings. Low doses of heparin can be prescribed after the risk of continued bleeding has abated. When the patient's condition has stabilized, increased activity, mobilization, and rehabilitation begin.

VI. CAUSE-SPECIFIC TREATMENT

Management of the cause of bleeding is a key component of the overall treatment for patients with intracranial hemorrhage.

A. Vascular malformations. Patients with a ruptured vascular malformation may be treated to prevent a second hemorrhage. Because the risk of early rebleeding is relatively low, treatment usually is delayed until the hematoma has reabsorbed. The options for treatment include surgical resection, endovascular administration of vascular occlusive materials, or focused radiation. Decisions are influenced by the size and location of the malformation and the number and caliber of the feeding arteries. Lesions in neurologically eloquent areas and those that are deep in the brain may not be surgically approachable. A high-flow malformation is also a problem because a postoperative state of hyperperfusion leading to hemorrhage or severe brain edema can follow resection. A staged series including both endovascular and surgical procedures can also be performed. Small and deep vascular malformations may be managed with focused, high-intensity radiation that leads to secondary fibrosis and gradual occlusion of the vessels. Some patients with very large malformations may not be treatable with any of the currently available modalities.

B. Aneurysms. Patients with ruptured aneurysms are vulnerable to recurrent hemorrhage and ischemic stroke (Table 37.8). Rebleeding is a largely fatal event that peaks during the first 24 hours, when the risk is approximately 4%. The overall risk of recurrent hemorrhage during the first 10 days approaches 20%. The symptoms of rebleeding are similar to those of the initial hemorrhage, and a CT will show more blood. The most effective measures to forestall rebleeding are direct surgical obliteration of the aneurysm by clipping or endovascular occlusion of the aneurysm by inserting coils. In general, the goal is to treat the patient as quickly as possible. The selection of endovascular or direct surgical treatment is influenced by the patient's condition, the location of the aneurysm, the presence of serious comorbid diseases, or the presence of vasospasm. Recent studies suggest that the morbidity associated with endovascular treatment is less than that accompanying surgical clipping.

Vasospasm is an arterial process that occurs almost exclusively in association with aneurysmal SAH. It is most likely to occur among patients with extensive subarachnoid blood found on CT. The progressive arterial narrowing peaks at 7 to 10 days after SAH. Thereafter, vasospasm gradually abates. The arterial narrowing causes hypoperfusion, which leads to brain ischemia. The symptoms of vasospasm are worsening headache,

TABLE 37.8 Management of Patients with Aneurysmal SAH

Prevention of recurrent hemorrhage
Surgical treatment—clipping
Endovascular placement of coils or balloon
Antihypertensive agents
Brief course of antifibrinolytic therapy
Prevention of vasospasm and ischemic stroke
Avoidance of dehydration, hyponatremia, and hypotension
Avoidance of use antifibrinolytic agents
Reduction of increased ICP
Nimodipine
60 mg by mouth or nasogastric tube every 4 hr
Hypervolemic hemodilution and drug-induced hypertension
Intra-arterial administration of vasodilator medications
Angioplasty

altered consciousness, and focal neurologic signs that wax and wane. Transcranial Doppler ultrasonography may detect alterations of flow velocities in major arteries before the clinical signs appear. These studies often are performed at regular intervals during the period of highest risk. Arteriography can be used to confirm the arterial narrowing. Nimodipine is efficacious in improving outcomes after SAH presumably by lessening the ischemic effects, and it is unclear whether the medication has any effect on vasospasm.

Hypervolemic hemodilution and drug-induced hypertension (3-H therapy) are prescribed to patients in whom ischemic symptoms develop. Although no controlled trials have shown the efficacy of this regimen, several studies report success with 3-H therapy. The regimen is rigorous and monitoring is critical because myocardial ischemia, congestive heart failure, and pulmonary edema are possible adverse experiences. The regimen can also promote recurrent aneurysmal rupture if the aneurysm has not been treated. Angioplasty or intra-arterial infusions of vasodilators have been used to treat patients with vasospasm who have not responded to other interventions.

Recommended Readings

Bederson, JB, Connolly ES Jr, Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke.* 2009;40:944–1025.

Dumont AS, Crowley RW, Monteith SJ, et al. Endovascular treatment of neurosurgical clipping of ruptured intracranial aneurysms: effect on angiographic vasospasm, delayed ischemic neurological deficit, cerebral infarction, and clinical outcome. *Stroke*. 2010;42:2519–2524.

Kowalski RG, Claassen J, Kreiter KT, et al. Initial misdiagnosis and outcome after subarachnoid hemorrhage. *JAMA*. 2004;291:866–869.

Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med.* 2008;358:2127–2137.

Mendelow AD, Gregson BA, Fernandes HM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial hematomas in the International Surgical Trial in Intracerebral Hemorrhage (STICH): a randomized trial. *Lancet*. 2005;365:387–397.

Molyneux AJ, Kerr RS, Yu LM, Clarke M, et al; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomize trial. *Lancet*. 2002;36:1267–1274.

Morgenstern LB, Hemphill JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010; 41: 2108–2129.

Stapf C, Mohr JP, Choi JH, Hartmann A, Mast A. Invasive treatment of unruptured brain arteriovenous malformations is experimental therapy. *Curr Opin Neurol*. 2006;19:63–68.

CHAPTER

38 Epilepsies in Children

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Approximately 3% of the population of the United States is expected to have epilepsy at some time during their lives. Among children, 2% to 5% have a febrile seizure during the first 5 years of life, 2% have a single afebrile seizure, and 0.5% have recurrent afebrile seizures.

Classification

Accurate characterization of epilepsy has practical significance. Differentiation between partial and generalized seizures is important for the appropriate choice of antiepileptic drug (AED) therapy and determination of possible etiology and prognosis. Epileptic syndromes are classified with particular reference to age at onset, etiologic factor, site of seizure onset, and prognosis. Chapter 6 provides clinical descriptions of the different types of seizures.

I. LOCALIZATION-RELATED (FOCAL, LOCAL, AND PARTIAL) EPILEPSIES AND SYNDROMES

Localization-related (focal, local, and partial) epilepsies and syndromes are characterized by partial seizures (simple or complex partial) arising from a focal cortical area with occasional progression to a secondarily generalized tonic–clonic seizure (GTCS). If this progression is rapid, the initial focal nature may be masked. A simple partial seizure is associated with intact consciousness, whereas during a complex partial seizure, consciousness is impaired. EEG shows focal epileptiform discharges overlying the epileptogenic region.

A. Idiopathic localization-related epilepsy with age-related onset represent a group of epileptic syndromes that constitute approximately one-fifth of all cases of epilepsy with onset before 13 years of age. Idiopathic epilepsy is characterized by genetic predisposition, focal (localization-related) seizures and EEG abnormalities, normal intellect and normal findings at neurologic examination and neuroimaging studies, and an excellent prognosis. Currently, the following syndromes are recognized by the International League Against Epilepsy.

1. **Benign childhood epilepsy with centrotemporal spikes (BCECTS).** This disorder was previously known as *benign rolandic epilepsy.*
   a. BCECTS accounts for 13% to 23% of all childhood epilepsies and 75% of all benign focal childhood epilepsy.
   b. **Age at onset** is between 3 and 13 years; peak age is 8 to 9 years.
   c. **Clinical features** include unilateral paresthesias and clonic activity of the tongue, lip and cheek, speech arrest, excess salivation, and occasional progression to a GTCS. Seizures usually are nocturnal, during sleep.
   d. **EEG** shows frequent, unilateral or bilateral, high-amplitude centrotemporal spikes with a horizontal dipole that are activated by sleep, superimposed on a normal background. Thirty percent have spikes only during sleep. Therefore, a sleep-deprived EEG to include sleep should be obtained if this diagnosis is suspected. Approximately 50% of close relatives may also have EEG abnormalities between ages 5 and 15 years. Only 12% of patients who inherit the EEG abnormality have seizures.

e. **Treatment** usually is unnecessary after the first or even the second seizure. AED therapy can be initiated if seizures are frequent or if they are sufficiently disturbing the patient or family. All major AEDs have been reported to be successful even in small doses, such as carbamazepine, oxcarbazepine, valproic acid, gabapentin, phenobarbital, and phenytoin.

f. **Prognosis** is excellent. Approximately 13% to 20% of patients have only a single seizure. Seizures usually resolve within 1 to 3 years of onset and almost always by 14 to 16 years of age. Approximately 1% to 2% persist into adult life.

2. **Benign occipital epilepsy (BOE).** Two forms include early onset type (Panayiotopoulos' type) and late onset type (Gastaut's type).

a. **BOE** occurs less frequently than BCECTS.

b. **Age at onset.** Early onset type—4 to 5 years, with female preponderance; late onset type—8 to 9 years, with both sexes equally affected.

c. **Clinical features.** Early onset type is characterized by ictal vomiting, eye deviation, often progressing to GTCS seizures, which are usually nocturnal. The late onset type is brief (a few seconds to 2 to 3 minutes) with mainly visual illusions (multicolored circles or spots) or blindness, followed by hemiclonic convulsions and postictal headaches. Consciousness may be preserved, but it is impaired if the seizure secondarily generalizes. BOE is often misinterpreted as basilar (Bickerstaff's) migraine.

d. **EEG** shows occipital paroxysms of high amplitude, often bilateral sharp or spike–slow-wave complexes attenuating with eye opening and activated by sleep. Generalized or centrotemporal spike waves are found in one-third of all cases.

e. **Treatment** is similar to that of patients with BCECTS.

f. **Prognosis.** BOE carries a good prognosis, although it is not as benign as BCECTS. Clinical remission rates vary from 60% to 90%.

Two syndromes have been recognized among adult patients—autosomal dominant nocturnal frontal lobe epilepsy and benign familial temporal lobe epilepsy.

B. **Symptomatic localization-related epilepsy.** Most forms of localization-related epilepsy are symptomatic or acquired. Clinical manifestations depend on the anatomic location of the epileptogenic focus. Temporal lobe seizures (complex partial seizures) are the most common type of symptomatic partial seizures. See Chapter 6.

II. GENERALIZED EPILEPSIES AND SYNDROMES

Generalized epilepsies and syndromes are characterized by seizures that are generalized from onset, usually associated with impairment of consciousness and generalized epileptiform discharges on EEG reflecting involvement of both hemispheres. They include absence seizures, atypical absence seizures, myoclonic seizures, GTCS, atonic seizures, tonic seizures, clonic seizures, and infantile spasms.

A. **Idiopathic generalized epilepsy with age-related onset.** In these disorders, which are listed in the order of age of appearance, the seizures and EEG abnormalities are generalized from the onset. Intellect and findings at neurologic examination and neuroimaging are normal (idiopathic). There is a genetic predisposition with no other identifiable etiologic factor.

1. **Benign familial neonatal convulsions (BFNC).** This is a rare, autosomal dominant form of epilepsy with a genetic defect localized to chromosome 20q and 8q. The genes encode voltage-gated K^+ channels expressed in the brain (KCNQ2 and KCNQ3). Seizures occur during the first week of life, usually the second or third day. Diagnosis requires family history of neonatal seizures and exclusion of other causes such as infection, metabolic, toxic, or structural abnormalities. Approximately 10% develop subsequent nonfebrile seizures.

2. **Benign idiopathic neonatal seizures (fifth-day fits).** Seizures occur on the fifth day of life without known cause and generally cease within 15 days. The neonate is neurologically normal, and prognosis is good with no seizure recurrence. Subsequent psychomotor development is normal.

3. **Benign myoclonic epilepsy in infancy.**
   a. **Age at onset** is 4 months to 3 years, typically within the first year.
   b. **Clinical features.** Brief, generalized myoclonic seizures usually involving the head and upper extremities occur several times daily in an otherwise normal child, usually with a family history of epilepsy.
   c. **EEG** shows brief, generalized bursts of spike–polyspike wave activity.
   d. **Treatment.** Valproic acid is the drug of choice. Clonazepam can be used if valproic acid is ineffective.
   e. **Prognosis.** Response to treatment is good. Occasionally, some psychomotor delay and behavioral abnormalities may persist.
4. Epilepsy with myoclonic astatic seizures (Doose syndrome).
5. **Childhood absence epilepsy (pyknolepsy).** See Chapter 6.
6. **Juvenile absence epilepsy.** See Chapter 6.
7. **Juvenile myoclonic epilepsy (impulsive petit mal) of Janz.** See Chapter 6.
8. **Epilepsy with GTCS on awakening.** See Chapter 6.
9. Generalized epilepsy with febrile seizures plus (GEFS+).
   a. Autosomal dominant disorder manifesting with febrile seizures in children <1 year of age, which persist beyond 5 to 6 years, when nonfebrile seizures also occur. Family history of febrile seizures is necessary to the diagnosis. It has been linked to a number of gene loci (SCN1A, SCN1B, and GABRG2). With inherited missense mutations of SCN1A GEFS+ occurs, while de novo truncating mutations result in severe myoclonic epilesy of infancy (SMEI; Dravet's syndrome).

B. Symptomatic or cryptogenic generalized epilepsy. These disorders, which are listed in order of age of appearance, include generalized epilepsy syndromes secondary to known or suspected disorders of the CNS (symptomatic) or to disorders, the causes of which are hidden or occult (cryptogenic).

1. **Infantile spasms (West's syndrome, salaam seizures, and jackknife seizures).**
   a. **Etiology.** With the availability of newer neuroimaging techniques, only 10% to 15% of cases are cryptogenic. In symptomatic cases, there is evidence of previous brain damage (mental retardation, neurologic and radiologic evidence, or a known etiologic factor) (Table 38.1).
   b. **Age at onset.** Onset occurs in infancy (peak 4 to 8 months).
   c. **Clinical features** compose the triad of infantile spasms, mental retardation, and hypsarrhythmia. Infantile spasms occur in clusters, frequently during drowsiness and on awakening, characterized by brief nodding of the head associated with extension or flexion of the trunk, and often of the extremities. They occur rapidly, suggestive of a startle reaction. They can be flexor (salaam attacks), extensor, or most commonly, mixed spasms. They are almost always associated with arrested development.

TABLE 38.1 Causes of Secondary Generalized Epilepsy Syndromes (Infantile Spasms and LGS)

Idiopathic, Cryptogenic
Symptomatic
Perinatal factors: hypoxic–ischemic encephalopathy, hypoglycemia, and hypocalcemia
Infection: intrauterine infection (toxoplasmosis, rubella, and cytomegalovirus, herpes), meningoencephalitis
Cerebral malformation: holoprosencephaly, lissencephaly, and Aicardi's syndrome
Vascular: infarction, hemorrhage, and porencephaly
Neurocutaneous syndromes: tuberous sclerosis complex, Sturge–Weber's syndrome, incontinentia pigmenti, and others (e.g., neurofibromatosis)
Metabolic disease: nonketotic hyperglycinemia, pyridoxine deficiency, aminoacidopathy (phenylketonuria, maple syrup urine disease)
Degenerative disorder: neuronal ceroid lipofuscinosis (Batten's disease)
Chromosomal disorders: Down's syndrome, Angelman's syndrome (happy puppet syndrome: abnormality in chromosome 15q11–13, seizures, developmental delay, dysmorphic features, and paroxysms of inappropriate laughter)

d. **EEG** shows hypsarrhythmia—chaotic, high-amplitude, disorganized background with multifocal independent spike-and-wave discharges. Intravenous (IV) pyridoxine (vitamin B_6) should be administered in a dose of 100 mg during the EEG to exclude pyridoxine-dependent infantile spasms.

e. **Treatment.**
   (1) Underlying conditions are managed as identified.
   (2) **Adrenocorticotropic hormone (ACTH).** Opinions vary regarding dosage and duration of ACTH therapy, ranging from high-dose therapy (150 IU/m^2/day) to low-dose therapy (20 to 40 IU/day). We recommend starting at 40 to 80 units per day administered intramuscularly and continuing for 3 to 4 weeks, or for a shorter period if an early positive clinical response is observed. The dosage is then slowly decreased approximately 20% per week over 6 to 9 weeks. If seizures recur during withdrawal, the dosage should be increased to the previous effective level. ACTH therapy is initiated in the hospital under the guidance of a pediatric neurologist. Parents should be taught the injection technique with systematic rotation of the injection site.
   (3) **Side effects of ACTH therapy** are irritability, hyperglycemia, hypertension, sodium and water retention, potassium depletion, weight gain, gastric ulcers, occult gastrointestinal bleeding, suppression of the immune system, infection, congestive heart failure, and diabetic ketoacidosis.
   (4) **Laboratory tests before initiation of ACTH therapy** include baseline EEG, serum electrolytes, blood urea nitrogen (BUN), serum creatinine, glucose, urinalysis, CBC, chest radiograph, and tuberculin skin test.
   (5) **Laboratory tests performed weekly during ACTH therapy** include serum electrolytes, blood glucose, stool guaiac, and monitoring of weight and blood pressure.
   (6) **Concomitant management.** An antacid or a histamine H_2 receptor antagonist (ranitidine) should be administered during ACTH therapy.

f. **Alternative treatment.**
   (1) **Prednisone** may be substituted when ACTH cannot be administered because parents cannot or will not learn to give injections. It is administered orally at 2 to 3 mg/kg/day for 3 to 4 weeks and gradually withdrawn in a schedule similar to ACTH withdrawal.
   (2) **Other AEDs.** Vigabatrin has the best response rates in patients with tuberous sclerosis. Valproic acid (usually at high therapeutic levels of 75 to 125 μg per ml), topiramate, zonisamide, and clonazepam have also been reported to be effective. Nitrazepam and clobazam have also been tried, but have not yet been approved in the United States.
   (3) **Excisional surgery** of the region of cortical abnormality defined at EEG, MRI, and positron emission tomography (PET) is being performed on children with infantile spasms intractable to medical therapy, but only in specialized centers. Further studies are needed to determine which patients may benefit from surgery and whether long-term development is significantly improved after surgical intervention.

g. **Prognosis.** West's syndrome has a high morbidity, with a 90% incidence of mental retardation. From 25% to 50% of cases evolve into Lennox–Gastaut's syndrome (LGS), infantile spasms transforming to other seizure types (GTCS, myoclonic, and tonic seizures) over subsequent years. Favorable prognostic indicators are as follows:
   (1) Cryptogenic spasms have a better prognosis than symptomatic cases.
   (2) Normal development and neurologic examination before the onset of spasms.
   (3) Short duration of seizures before control.

2. Lennox–Gastaut's syndrome.

a. **Etiology.** A large number of patients have a history of infantile spasms. About 10% to 40% of cases are cryptogenic. In 60% to 90% of symptomatic cases, a specific cause, usually perinatal insult, is found (Table 38.1).

b. **Age at onset** is 1 to 8 years of age, with peak between 3 and 5 years.

c. **Clinical features** are seizures of multiple types, typically tonic, atypical absence, atonic,

and myoclonic seizures but also GTCS, and partial seizures. Seizures are often frequent and intractable to medical treatment. Most patients have cognitive dysfunction.

d. **EEG** shows slow background activity, generalized, bisynchronous, 2 to 2.5 Hz spike–slow-wave discharges activated by sleep, generalized paroxysmal fast spike activity (10 Hz), and other multifocal epileptiform abnormalities.

e. **Treatment.**

(1) AEDs. **Valproic acid** is effective against all the different types of seizures associated with LGS. However, these seizures often are intractable, and valproic acid may have to be used in combination with other AEDs. Ethosuximide, **lamotrigine, and topiramate** have successfully demonstrated efficacy as adjunctive therapy in LGS. Zonisamide and levetiracetam have also been reported to be effective. Felbamate, though effective, is infrequently used because of severe side effects such as aplastic anemia and acute liver failure. Phenytoin and phenobarbital may be helpful in controlling the associated GTCS. Benzodiazepines (clonazepam, nitrazepam, and clobazam) can be used, but may be associated with side effects of decreased alertness and drowsiness, which are associated with increased seizure frequency. IV diazepam or lorazepam may induce tonic seizures, and carbamazepine can exacerbate absence seizures.

(2) **Ketogenic diet** may be effective for patients with otherwise intractable seizures. Benefits include fewer seizures, less drowsiness, and fewer concomitant AEDs.

(3) **ACTH** has been found to be effective in the treatment of some patients.

(4) **Psychological support** for the child and family. A prescription for protective helmets to prevent head injuries in patients with drop attacks is helpful.

(5) **Surgical procedures** such as corpus callosotomy, hemispherectomy, and rarely resection of a localized lesion have been tried with variable results. Vagal nerve stimulation is also effective with at least 50% reduction in seizure frequency in follow-up periods as long as 5 years.

3. **Symptomatic seizures.** Myoclonic seizures are difficult to differentiate from nonepileptic myoclonus. However, characteristic epileptiform discharges associated with myoclonic jerks in myoclonic epilepsy help differentiate the two.

a. **Early myoclonic encephalopathy.** Multiple causes include inborn errors of metabolism such as nonketotic hyperglycinemia, methymalonic academia, and proprionic academia. Early myoclonic encephalopathy is characterized by the onset of medically intractable myoclonic seizures and partial seizures in early infancy before 3 months of age, burst suppression on EEG, and very poor prognosis including profound neurologic impairment or death in the first year of life.

b. **Early infantile epileptic encephalopathy (Ohtahara's syndrome)** is characterized by an early onset of tonic spasms within the first few months of life, which are medically intractable. Myoclonic seizures are rare. The suppression-burst pattern on the EEG is present during waking and sleep states. MRI demonstrates severe developmental anomalies such as hemimegalencephaly, porencephaly, and Aicardi's syndrome. The prognosis is very poor.

c. **SMEI (Dravet's syndrome)** represents 3% to 5% of all epilepsies starting in the first year of life. The disorder begins in the first year of life as febrile seizures, followed by myoclonic seizures, atypical absences, and convulsive seizures between 1 and 4 years of age. The child is initially normal, but cognition becomes progressively impaired. EEG shows generalized spike and polyspike–slow-wave activity, focal or multifocal spikes. Photosensitivity is seen in 40%. Lamotrigine may induce worsening of seizures. The seizures are medically intractable, but may respond to valprioc acid, topiramate, and clobazam. Stiripentol has also proved to be effective. A link between SMEI and GEFS+ has been identified in several families. De novo truncating mutations of the SCN1A gene on chromosome 2p24 in coding for the neuronal voltage-gated sodium channel $\alpha 1$ subunit have been found in SMEI.

d. **Symptomatic myoclonic epilepsy** is associated with specific progressive neurologic diseases such as Lafora's disease, Baltic myoclonus (Unverricht–Lundborg's disease), neuronal ceroid lipofuscinosis (Batten's disease), sialidosis, mitochondrial encephalomyopathy, and Ramsey–Hunt's syndrome.

III. EPILEPSIES AND SYNDROMES UNDETERMINED WHETHER FOCAL OR GENERALIZED

A. Neonatal seizures. Seizures occur most frequently in the neonatal period than at any other time in childhood, with an incidence of 1.5 to 5.5 per 1,000 live births.

1. **Clinical features.** Neonatal seizures (occurring between birth and 2 months) are more fragmentary than are seizures among older children. GTCS do not occur in neonates. Common causes are outlined in Table 38.2. Neonatal seizures are classified as follows:
   a. **Seizures associated with electrographic signatures** include focal and multifocal clonic seizures, focal tonic seizures, generalized myoclonic seizures, and rarely, apnea. These seizures usually are associated with focal structural lesions (infarction or hemorrhage), infection, or metabolic abnormalities (hypoglycemia or hypocalcemia).
   b. **Seizures not associated with electrographic signatures** include generalized tonic seizures, focal and multifocal myoclonic seizures, and subtle seizures (oral–buccal–lingual movements, bicycling movements, and some rhythmic ocular movements such as horizontal eye deviation). These seizures usually are observed among lethargic, comatose neonates with poor prognoses, such as those with severe hypoxic ischemic encephalopathy.
2. **Evaluation.** Neonatal seizures should be managed in a neonatal intensive care unit by experienced personnel, including a pediatric neurologist and a neonatologist.
   a. **History and examination.** History of maternal illness, infection, or drug and alcohol abuse during pregnancy should be obtained. Family history of neonatal seizures is suggestive of BFNC. Evaluation of the skin, anterior fontanel, and neurologic and ophthalmologic examinations should be performed. Presence of skin rash and chorioretinitis may suggest toxoplasmosis.
   b. **Laboratory data** include CBC, serum glucose, electrolytes, BUN, serum creatinine, liver function tests, magnesium, calcium, phosphate, ammonia, lactate, pyruvate, biotinidase, lumbar puncture (LP) to rule out CNS infection and subarachnoid hemorrhage (SAH), titres for toxoplasmosis, rubella, cytomegalovirus, herpes, and HIV (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes [TORCH]), and Venereal Disease Research Laboratory. Additional studies such as plasma amino acids and very-long-chain fatty acids, urinalysis for amino acids and organic acids, CSF lactate, and neurotransmitters may be indicated if metabolic disorders are suspected. Ultrasonography of the head at bedside to rule out intracranial hemorrhage and a non-contrast-enhanced CT or MRI of the head can be performed when the neonate's condition is stable. EEG is useful for the diagnosis of subclinical seizures and assessment of prognosis. EEGs with low voltage, burst-suppression or isoelectric patterns suggest poor prognosis.
3. **Treatment.**
   a. **Management of underlying cause** such as CNS infection or specific metabolic abnormality (hypoglycemia, hypocalcemia, or hypomagnesemia).
   b. **Phenobarbital,** the initial drug of choice is administered IV as a loading dose of 20 mg per kg followed by additional 5 to 10 mg per kg boluses as required to

TABLE 38.2 Common Causes of Neonatal Seizures

Hypoxic–ischemic encephalopathy
Metabolic: hypocalcemia, hypoglycemia, hyponatremia, hypernatremia, and hypomagnesemia
Trauma: subdural hematoma and intracerebral hemorrhage
Infection: sepsis, meningitis (group B ß-hemolytic *Streptococcus*), encephalitis, TORCH, HIV
Congenital abnormalities: lissencephaly, holoprosencephaly, and other migrational disorders
Inborn errors of metabolism: amino acid disturbances (urea cycle disorder and nonketotic hyperglycinemia), pyridoxine dependency, phenylketonuria, galactosemia
Drug withdrawal: heroin, barbiturate, methadone
Neurocutaneous and genetic syndromes: tuberous sclerosis complex, ARX (Aristaless-related homeobox) mutations that are associated with congenital malformations such as lissencephaly
BFNC, fifth day fits

Abbreviation: ARX, aristaless-related homeobox.

achieve serum levels between 20 and 40 μg per ml and to control clinical seizures. Maintenance dose of 3 to 4 mg/kg/day given twice a day is usually sufficient because phenobarbital has a relatively long half-life in neonates. Cardiorespiratory monitoring is important because IV administration can be associated with respiratory depression and hypotension.

c. **Phenytoin** is added if a phenobarbital level of 40 mg per ml is not sufficient to control seizures. An IV loading dose of 20 mg per kg results in serum levels ranging from 15 to 20 μg per ml, followed by a maintenance dose of 3 to 4 mg/kg/day given twice a day. Phenytoin is infused slowly with cardiac monitoring, because it can cause cardiac arrhythmias and hypotension. It is alkalotic and may lead to local venous thrombosis or tissue irritation. Use of fosphenytoin reduces these risks.

d. **Benzodiazepines** are third-line treatments. Lorazepam 0.05 to 0.1 mg per kg administered IV enters the brain rapidly, being effective in <5 minutes. Being less lipophilic, it does not redistribute from the brain as rapidly as does diazepam, the duration of action being 6 to 24 hours. Lorazepam is less likely to produce respiratory depression or hypotension than diazepam.

e. **Pyridoxine** (100 mg IV) administered during EEG monitoring stops seizures and normalizes the EEG within minutes in the rare patient with pyridoxine-dependent seizures.

B. Acquired epileptic aphasia (Landau–Kleffner's syndrome) is characterized by acquired aphasia, including verbal auditory agnosia, rapid reduction of spontaneous speech, and behavioral and psychomotor disturbances, with onset during the first decade of life. Seizures (generalized and focal) and EEG abnormalities, including multifocal spikes and spike–wave discharges commonly in the temporal or parietooccipital regions, are activated by sleep. The ultimate outcome is still unclear.

IV. SPECIAL SYNDROMES

A. Situation-related seizures.

1. Febrile seizures.

a. **Incidence.** Febrile seizures occur in 2% to 5% of young children.

b. **Age at onset** ranges from 3 months to 5 years (peak 18 months to 2 years). The disorder is familial.

c. **Clinical features** manifest within the first few hours of acute infection, usually associated with the rising phase of the temperature curve. They are typically associated with viral upper respiratory tract, gastrointestinal, and middle ear infections. Bacterial infection is rarely associated with febrile seizures. Intracranial infection and other defined causes such as dehydration and electrolyte imbalance should be excluded.

(1) **Simple febrile seizures** present as single, brief (<15 minutes), GTCS. They represent 80% to 90% of all febrile seizures.

(2) **Complex febrile seizures** are prolonged (>15 minutes), have focal features (focal onset or postictal Todd's paralysis), and more than one seizure occurs within 24 hours.

d. **Evaluation.** LP is indicated unless the possibility of meningitis can be confidently eliminated clinically. It should be performed for all children younger than 18 months, because they may not always have meningeal signs in the face of meningitis. If in doubt, err on the side of performing LP. It should be strongly considered in the evaluation of infants and children who have received antibiotic treatment because such treatment can mask evidence of meningitis. Serum electrolyte and glucose tests should be performed.

e. **Acute management of seizures.**

(1) Prolonged febrile seizures can be treated with IV lorazepam, diazepam, or phenobrbital.

(2) Rectal diazepam gel (Diastat 0.2 to 0.5 mg per kg) can be administered at the onset of a seizure in children with history of prolonged seizures.

(3) Any underlying infection or fever should be controlled.

f. **Long-term management of seizures.** No treatment is necessary if the patient has isolated simple febrile seizures without major risk factors for recurrence.

(1) Daily phenobarbital treatment reduces the risk of recurrent febrile seizures and may be used for patients with complex febrile seizures that carry increased risk of later epilepsy. Because 90% of febrile seizures recur within 2 years, treatment should be continued for at least 2 years or for 1 year after the last seizure, whichever is longer. Valproic acid is the second choice because of an increased incidence of side effects, including liver toxicity, in this age group. Carbamazepine and phenytoin do not prevent recurrent febrile seizures.

(2) Some pediatric neurologists use oral diazepam, administered only when fever is present, and have found it effective in reducing the risk of recurrent febrile seizures. Side effects include lethargy, irritability, and ataxia.

g. **Prognosis.** Approximately 33% of children with febrile seizures have at least one recurrence, and 9% have three or more seizures. Remission occurs by 6 years of age in approximately 90% of children.

(1) Risk factors for recurrence include young age (<1 year) at initial seizure, seizures occurring with low grade fever, and a family history of febrile seizures.

(2) Risk factors for the development of epilepsy include complex febrile seizures, underlying developmental or neurologic abnormalities, and family history of nonfebrile seizures. Patients with two risk factors have a 13% chance of developing epilepsy.

2. **Seizures related to identifiable situations** such as use of drugs (stimulants or neuroleptics) or alcohol, and sleep deprivation.

B. Isolated, apparently unprovoked epileptic events. Treatment is not indicated unless there are significant risk factors for recurrence.

C. Epilepsy characterized by specific modes of seizure precipitation includes seizures occurring in response to discrete or specific stimuli (reflex epilepsy), such as reading epilepsy, hot water epilepsy, and arithmetic epilepsy.

D. Chronic progressive epilepsia partialis continua of childhood (Kojewnikoff's syndrome) is thought to be a result of chronic encephalitis (Rasmussen's encephalitis). The cause is unknown. It is characterized by partial motor seizures, often associated with myoclonus, which are resistant to treatment. This condition results in progressive hemiplegia with unilateral brain atrophy and mental retardation.

Evaluation

Details regarding histories, physical examinations, and studies such as EEG and neuroimaging are discussed in Chapter 6. Important aspects of the evaluation with respect to children follow. Determine whether the paroxysmal events in question are in fact epileptic. They should be differentiated from nonepileptic paroxysmal events in children.

I. SPECIFIC PREDISPOSING FACTORS FOR CHILDHOOD SEIZURES

A. Birth history.

1. **Prenatal.** Prematurity, complications (e.g., toxemia or premature labor), medications, smoking, and alcohol and drug abuse.
2. **Perinatal.** Low birth weight, low Apgar scores, and complications of labor and delivery.
3. **Postnatal.** Intensive neonatal respiratory care, complications such as meningitis, intraventricular hemorrhage, and exchange transfusions.

B. Developmental history. Learning disabilities, attention deficit, and developmental regression.

II. PHYSICAL EXAMINATION

A. Head circumference. Microcephaly and macrocephaly are associated with various neurologic disorders.

B. Height and weight abnormalities.
C. Dysmorphic features associated with chromosomal anomalies, storage diseases, or brain malformations.
D. Skin. Café au lait spots are seen in neurofibromatosis, hypopigmented macules and adenoma sebaceum in tuberous sclerosis, and facial hemangiomas in Sturge–Weber's syndrome.
E. Hair. Broken hair and alopecia suggest metabolic disorders (biotinidase deficiency, Menkes' syndrome, and argininosuccinic aciduria).
F. Mental status and developmental milestones. Loss of previously attained milestones may be indicative of a neurodegenerative disease (e.g., Retts' syndrome), whereas delays in achieving developmental milestones reflect static encephalopathies (e.g., cerebral palsy). Presence of anxiety, depression, and stressors such as family conflict may lead to the diagnosis of psychogenic seizures.
G. Systemic exam. Organomegaly may suggest a storage disease or an inborn error of metabolism.

III. LABORATORY TESTING

In addition to EEG and MRI of the head, other important studies in children include the following:

A. Chemical and metabolic screening. Electrolytes, glucose, calcium, magnesium, hepatic and renal function tests, and toxic screening for possible drug ingestion. Specific metabolic or neurodegenerative disorders may be diagnosed with tests such as thyroid function tests, urinalysis for amino acids, organic acids, lysosomal enzymes (mucopolysaccharidosis and Batten's disease), and very-long-chain fatty acids (peroxisomal disorders such as adrenoleukodystrophy). Elevation of serum prolactin levels is seen with GTCS, may be normal with focal seizures, and can help differentiate seizures from nonepileptiform paroxysmal disorders. Prolactin should be measured within 30 minutes after an episode and compared with baseline values.
B. LP is indicated if there are signs of acute CNS infection or inflammation (e.g., fever or stiff neck). It is indicated for all children younger than 18 months with a history of fever and seizures, because clinical signs of CNS infection may be absent. It should be performed on all febrile patients with new-onset seizures.
C. Chromosomal analysis is indicated if dysmorphic features suggest chromosomal abnormalities.
D. Genetic testing. Mutations in SCN1A have been associated with SMEI and GEFS+, and mutations in SCN1B, with GEFS+. Mutations in KCNQ2 gene have been associated with BFNC.
E. Skin biopsy is performed to diagnose certain metabolic diseases such as Batten's disease.
F. Simultaneous prolonged video EEG monitoring in an epilepsy unit can help determine the exact nature of paroxysmal events if they cannot be defined with routine EEG.

Treatment

I. SINGLE SEIZURE

Approximately 9% of the population has a seizure sometime during their lives, and approximately 3% have more than one seizure. The risk of recurrence is highest in the first year after a single seizure. It is low if the patient has normal findings at neurologic examination, a single GTCS with a negative family history, normal findings at neuroimaging, and a normal or mildly slow EEG.

A. Indications for treatment.
1. Clear-cut epileptiform abnormalities at EEG.
2. Lesions on CT scans or MR images.
3. Abnormal findings at neurologic examination that suggest previous brain damage.

4. Active CNS infection (encephalitis, meningitis, or abscess).
5. Status epilepticus as the first seizure.
6. Certain types of seizures, including infantile spasms, LGS, and focal seizures.
7. Unprovoked or asymptomatic single seizure with history suggesting that one may have occurred earlier.

B. Treatment is not indicated when seizures are provoked by a correctable metabolic disturbance (glucose or electrolyte abnormalities), sleep deprivation, exposure to drugs or alcohol, febrile illness, or physical or emotional stress. In such cases, the underlying disturbance should be corrected.

II. GENERAL PRINCIPLES OF TREATMENT

A. Choice of appropriate drug should be based on the clinical description of the seizures (Table 38.3). This choice may be influenced by other factors, such as the patient's age, associated medical illnesses, and economic circumstances.

B. Monotherapy. Approximately 75% to 80% of children should respond to monotherapy. If the first drug is ineffective, start a second AED with a different mechanism of action and low potential for adverse effects and drug interactions. After therapeutic levels are achieved, gradually withdraw the first drug.

C. Polypharmacy is indicated only if monotherapy with at least two first-line AEDs fails, and should be initiated only after consultation with a pediatric neurologist. Associated problems include drug interactions, difficulties in acquiring therapeutic levels of either drug despite use of adequate doses, increased risks of toxicity, increased cost, and reduced compliance.

D. Simplify medication schedule. Decreasing the number of doses improves compliance.

E. Avoid sedative anticonvulsants such as benzodiazepines, especially for patients with secondary generalized epilepsy syndrome, because increased sedation can cause result in increased seizures.

F. Maintain a seizure diary. Record seizure frequency, medication dosages and levels, and occurrence of side effects, if any.

TABLE 38.3 Drugs for the Management of Epilepsy

Seizure Type	First-Line Drug	Second-Line Drug
Partial		
Simple partial, complex partial, secondary GTCS	Carbamazepine, oxcarbazepine, valproic acid, topiramate, zonisamide	Lamotrigine, levetiracetam, phenytoin, phenobarbital, primidone
Generalized		
Absence (typical and atypical)	Ethosuximide, valproic acid	Lamotrigine, clonazepam, acetazolamide, felbamate
Myoclonic	Valproic acid	Levetiracetam, zonisamide, acetazolamide, clonazepam, clorazepate
Tonic–clonic	Valproic acid, phenytoin	Lamotrigine, topiramate, rufinamide, levetiracetam, phenobarbital, primidone, felbamate
Atonic	Valproic acid	Lamotrigine, rufinamide, topiramate, levetiracetam clonazepam, clorazepate, felbamate

Phenobarbital and valproic acid are used for atypical febrile seizures. Fosphenytoin and phenobarbital IV are used for status-epilepticus.

G. **AED level** should be checked just before a dose, preferably the morning dose to obtain the lowest (trough) level and at a consistent time to avoid misinterpretation of fluctuations. CBC and aspartate aminotransferase levels are checked every 1 to 2 months initially and then every 6 months after a steady dosage has been established. AED blood level should be checked.
1. After starting a medication, to aid in initial titration of dose to achieve a therapeutic level.
2. After making a major change in drug dosage.
3. If seizures recur with the usual dosage of AED.
4. If seizures persist despite "correct therapy."
5. If symptoms of toxicity develop.
6. If noncompliance is suspected.

H. **Repeat EEG** during therapy if there is a change in the character of the seizures or if the child has been seizure-free for a considerable period to help decide whether medications can be withdrawn.

III. DRUG THERAPY

The following information serves as a broad guideline for AEDs commonly used to treat children. Indications are listed in Table 38.3. Details regarding their metabolism, side effects, and interactions are discussed in detail in Chapter 39.

A. **Phenytoin (Dilantin; Parke–Davis).**
1. **Administration** (5 to 8 mg/kg/day). Children have shorter elimination half-lives than adults and should be given two divided doses. Phenytoin has nonlinear elimination kinetics. Therefore, small increases in dose after therapeutic levels of 10 to 20 μg per ml have been achieved resulting in large increases in plasma levels and toxicity.
2. **Formulation.** Capsules: Dilantin, 30 and 100 mg; Infatabs: 50 mg; Phenytoin 100, 200, 300 mg (extended release); suspension: 125 mg per 5 ml and 30 mg per 5 ml. Dilantin suspension is not recommended for routine use because it is unreliable. Parenteral: injectable sodium phenytoin (Dilantin and generic 50 mg per ml), fosphenytoin (Cerebyx [Pfizer] 50 mg phenytoin equivalent [PE] per ml).
3. **Side effects.** Dose-related side effects are nystagmus, ataxia, and drowsiness. Gingival hypertrophy (20% to 50% of patients) requiring more frequent dental cleaning, hirsutism, coarsening of features, blood dyscrasias, Stevens–Johnson's syndrome, lymphadenopathy, SLE, and megaloblastic anemia can also occur. Long-term administration has been associated with vitamin D, vitamin K, and folic acid deficiency. Fetal hydantoin syndrome is characterized by craniofacial anomalies, hypoplasia of distal phalanges, intrauterine growth retardation, and mental deficiency. The term has been replaced by "fetal anticonvulsant syndrome," because the malformations are also seen in children of mothers who have been exposed to a variety of other AEDs such as valproic acid, carbamazepine, and phenobarbital as well.

B. **Carbamazepine (Tegretol, Tegretol XR; Novartis. Carbatrol, Shire–Richwood).**
1. **Administration.** Start at 5 mg/kg/day and increase by 5 mg/kg/day every 5 to 7 days to a maximum of 10 to 30 mg/kg/day in bid (for sustained release preparations) and tid doses to achieve therapeutic blood levels of 4 to 12 μg/ml. Carbamazepine can exacerbate absence, atypical absence, and myoclonic seizures.
2. **Formulation.** Tablets: 200 mg; chewable tablets: 100 mg; elixir: 100 mg per 5 ml; sustained-release preparations: Tegretol XR: 100, 200, and 400 mg; Carbatrol extended-release capsules: 200 and 300 mg. If oral administration is contraindicated, Tegretol suspension (100 mg per 5 ml) can be given rectally, diluted 1:1 with water in an enema at a dose of 10 to 30 mg per kg to attain therapeutic levels.
3. **Side effects.** Dose-related side effects are sedation, blurred vision, and leukopenia. Agranulocytosis, aplastic anemia, and syndrome of inappropriate antidiuretic hormone secretion also may occur. There is a 0.5% to 1% risk of spina bifida and other anomalies associated with the fetal anticonvulsant syndrome, with first-trimester exposure to carbamazepine.

C. Oxcarbazepine (Trileptal; Novartis).

1. **Administration.** 10 mg/kg/day, to be increased by the same amount weekly to 20 to 40 mg/kg/day, in two divided doses to achieve therapeutic blood level of 10 to 35 mg/L. It has less potential for drug interactions because of lack of auto-induction.
2. **Formulation.** Tablets: 150, 300, and 600 mg; suspension: 300 mg per 5 ml.
3. **Side effects.** Somnolence, dizziness, and headaches. Cross allergy between carbamazepine and oxcarbazepine occurs in 35% of cases. Hyponatremia is more frequent than with carbamazepine, seen in 2.5% of patients.

D. Phenobarbital (various generic formulations).

1. **Administration.** 3 to 8 mg/kg/day in a single daily dose or two divided doses to achieve therapeutic blood levels of 15 to 40 μg/ml. The serum half-life increases with age. It is 20 to 65 hours for patients younger than 10 years and 64 to 140 hours for those older than 15 years. Therefore, children need higher maintenance dosages of 4 to 8 mg/kg/day; adults need only 1 to 2 mg/kg/day. It can exacerbate absence, atypical absence, and myoclonic seizures, if used for GTCS in patients with generalized epilepsy.
2. **Formulation.** Tablets: 15, 30, 60, and 100 mg; elixir: 20 mg per 5 ml. Parenteral: injectable sodium phenobarbital (60 and 130 mg per ml).
3. **Side effects.** Hyperactivity, sedation, learning disabilities, personality changes, and Stevens–Johnson's syndrome. Long-term administration has been associated with vitamin D, vitamin K, and folic acid deficiency.

E. Valproic acid (Depakene, Depakote, Depacon; Abbott).

1. **Administration.** Start at 10 to 15 mg/kg/day or lower, and gradually increase to a maximum of 60 mg/kg/day in three divided doses to achieve therapeutic blood levels of 40 to 100 μg per ml.
2. **Formulation.** Depakote (divalproex sodium): enteric-coated tablets, 125, 250, and 500 mg; sprinkles, 125 mg; extended release tablets, 250 and 500 mg. Depakene (valproic acid): capsules, 250 mg; syrup, 250 mg per ml. Parenteral IV preparation: Depacon (100 mg/ml) starting at 10 to 15 mg/kg/day increased 5 to 10 mg/kg/day/week to a maximum of 60 mg/kg/day infused over 60 minutes at a rate not to exceed 20 mg/minute. If oral administration is contraindicated (e.g., paralytic ileus), Depakene elixir (250 mg per 5 ml) can be given rectally, diluted 1:1 with water in an enema at a dose of 20 mg per kg to attain therapeutic levels of 40 to 100 μg per ml.
3. **Side effects.** Dose-related side effects include nausea, vomiting, and gastric irritation, minimized with the use of the sprinkle or enteric-coated preparation or administration after meals. Other side effects include weight gain, alopecia, tremor, and thrombocytopenia. Idiosyncratic toxicity includes panceratitis (0.5%) and liver failure. Liver failure is more common among children younger than 2 years, and with polypharmacy. It can be a fulminant progressive failure or a subacute gradually progressive failure. Valproic acid is therefore contraindicated in the treatment of children with preexisting hepatic damage, organic aciduria, or carnitine deficiency. Carnitine (Carnitor, 10% solution or 330 mg tablet) should be administered 50 mg/kg/day in two or three divided doses in conjunction with valproic acid to children undergoing long-term, high-dose therapy with poor nutrition (e.g., cerebral palsy). Baseline liver function and serum ammonia should be checked before starting valproic acid and at least monthly for the first 4 to 6 months while this medication is being given. There is a risk of cognitive impairment and a 2% risk of neural tube defects such as spina bifida and, less commonly, myelomeningocele in the fetus when valproic acid is used during pregnancy. It may be associated with increased risk of polycystic ovarian syndrome.

F. Lamotrigine (Lamictal; GlaxoSmithKline).

1. **Administration.** Co-administration of valproic acid increases the elimination half-life of lamorigine to 60 hours or more. Therefore, the dose needs to be adjusted. Children not taking valproic acid: initial dose of 0.6 mg/kg/day for 2 weeks, increased to 1 mg/kg/day for 2 weeks and thereafter, slowly titrated to a maximum of 5 to 15 mg/kg/day twice a day. Children taking valproic acid: initial dose of 0.15 mg/kg/day for 2 weeks, increased to 0.3 mg/kg/day for 2 weeks and slowly titrated to a maximum of 1 to 5 mg/kg/day twice a day. Therapeutic blood levels are 5 to 15 mg per ml.

2. **Formulation.** Chewable dispersible tablet: 2, 5, and 25 μg; tablets: 25, 100, 150, and 200 mg.
3. **Side effects.** Common adverse effects among children include somnolence, rash, vomiting, laryngitis, ataxia, and headache. Risk of skin rash in children is 1 in 100 to 200 as compared with 3 in 1,000 in adults and is seen within the first 6 weeks. The incidence of rash increases with higher initial doses and faster rates of dose escalation, especially among children receiving valproic acid.

G. Topiramate (Topamax; Ortho-McNeil).

1. **Administration.** Initiated at 0.5 to 1 mg/kg/day increased slowly to 4 to 9 mg/kg/day, given in two divided doses. Faster titration schedules have resulted in increased CNS side effects. Therapeutic blood levels are 3.4 to 16.6 μg per ml.
2. **Formulation.** Tablets: 25, 100, and 200 mg; sprinkle capsule: 15 and 25 mg.
3. **Side effects.** Somnolence, dizziness, ataxia, psychomotor slowing, speech disorder, paresthesia, kidney stones (1.5%), and weight loss. Decreased sweating usually with exposure to hot weather occurs more frequently in children. Acute myopia with secondary angle closure glaucoma has been reported, usually within the 1st month. New data suggest a higher risk of cleft palates in babies born to women taking the drug.

H. Levetiracetam (Keppra; UCB Pharma).

1. **Administration.** Initiated at 10 to 20 mg/kg/day, increased by 20 mg/kg/day every 2 weeks to reach a maximum dose of 40 to 60 mg/kg/day given twice a day. For children younger than 4 years, dose is determined by the doctor.
2. **Formulation.** Tablets: 250, 500, 750, and 1,000 mg; oral solution, 100 mg per ml.
3. **Side effects.** Fatigue, coordination problems, sleepiness, mood and behavior changes, such as anger, anxiety, depression, hostility, and irritability.

I. Zonisamide (Zonegran; Eisai).

1. **Administration.** 4 to 8 mg/kg/day divided twice a day. Therapeutic blood levels are 10 to 30 μg per ml. May be effective in myoclonic seizures as in progressive myoclonic epilepsies such as Unverricht–Lundborg's syndrome (Baltic myoclonus).
2. **Formulation.** Capsule: 25, 50, and 100 mg.
3. **Side effects.** Somnolence, dizziness, anorexia, headaches, confusion, cognitive impairment, oligohidrosis hyperthermia, and renal calculi (4%). Contraindicated in care of patients with hypersensitivity to sulfonamides (zonisamide is a sulfonamide).

J. Felbamate (Felbatol; Wallace).

1. **Administration.** Begin at 15 mg/kg/day for first week, 30 mg/kg/day for the second week, and 45 mg/kg/day divided three times a day from the third week (maximum 3,600 mg per day). Therapeutic blood levels are 50 to 110 μg per ml.
2. **Formulation.** Tablets: 400 and 600 mg; oral suspension 600 mg per 5 ml.
3. **Adverse effects.** Gastrointestinal side effects, including weight loss and anorexia, have been most prominent. Insomnia, somnolence, and fatigue also have occurred. Rash may occur if the patient is also taking Depakote. On August 1, 1994, a year after felbamate was approved, several cases of aplastic anemia and hepatotoxicity were reported. Physicians should restrict use of this drug only to children with severe epilepsy, especially LGS, which is refractory to other therapies with close monitoring of blood work according to specific guidelines.

K. Ethosuximide (Zarontin; Parke-Davis).

1. **Administration.** 20 to 40 mg/kg/day in two or three divided doses. Therapeutic blood levels are 40 to 100 μg per ml.
2. **Formulation.** Capsules: 250 mg; syrup: 250 mg per 5 ml.
3. **Side effects.** Gastric irritation, anorexia, nausea, vomiting, drowsiness, and hallucinations.

L. Primidone (Mysoline; Vintage).

1. **Administration.** 10 to 25 mg/kg/day in two divided doses. It undergoes hepatic conversion to phenobarbital and phenylethylmalonamide. Therapeutic blood levels are Primidone, 5 to 12 μg per ml; phenobarbital, 15 to 40 μg per ml.
2. **Formulation.** Tablets: 50 and 250 mg; suspension: 250 mg per 5 ml.
3. **Side effects.** Sedation, tremor, behavioral changes, and rash.

M. Clonazepam (Klonopin; Roche).

1. **Administration.** 0.03 to 0.10 mg/kg/day in two or three divided doses. Therapeutic blood levels are 0.02 to 0.08 μg per ml.

2. **Formulation.** Tablets: 0.5, 1, and 2 mg.
3. **Side effects.** Drowsiness, ataxia, irritability, diplopia, and drooling.

N. Clorazepate (Tranxene; Abbott).

1. **Administration.** 0.3 mg/kg/day, increased to a maximum of 3 mg/kg/day. Therapeutic blood levels are not established.
2. **Formulation.** Tablets: 7.5 mg.
3. **Side effects.** Drowsiness, dizziness, ataxia, and drooling.

O. Rufinamide (Banzel; Eisai)

1. **Administration.** Therapy should be initiated at 10 mg/kg/day in two divided doses, to be increased by 10 mg/kg increments every 2 days to a target dose of 45mg/kg/day or 3,200 mg/day whichever is less.
2. **Formulation. Tablets:** 200, 400 mg; suspension: 40 mg per ml
3. **Side effects:** Somnolence, headache, dizziness, fatigue, and somnolence. It is contraindicated in patients with familial short QT syndrome. Multi-organ hypersensitivity syndrome has been reported in association with Banzel's therapy, especially in children <12 years of age.

P. Vigabatrin (Sabril; Lundbeck).

1. **Administration.** Initial dosing of 50 mg/kg/day in two divided doses is increased by 25 to 50 mg/kg/day every 3 days up to a maximum of 150 mg/kg/day.
2. **Formulation.** 500 mg powder per packety for oral solution; 500 mg tablet.
3. **Side effects.** Progressive and permanent bilateral concentric visual field constriction has been noted in 30% or more patients. It can be mild to severe resulting in disability. It should therefore be withdrawn from a pediatric patient treated for infantile spasms who fails to show benefit within 2 to 4 weeks. Abnormal MRI signals have been noted in some, but they generally resolve with discontinuation of therapy. Anemia, somnolence, and weight gain have also been reported.

Q. Other antiepileptic medications available in the United States include tiagabine (Gabitril; Abbott), gabapentin (Neurontin; Parke-Davis), and pregabalin (Lyrica; Parke-Davis). Stiripentol and clobazam used for Dravet's syndrome are currently not approved in the United States.

R. Newer AEDs still under evaluation include ganaxolone, remacemide, and losigamone.

IV. PSYCHOSOCIAL ISSUES

A. Avoid risk factors such as fatigue and sleep deprivation. Seat belts and bicycle helmets should be worn to prevent head injuries that may lead to seizures.

B. Seizure precautions. Bathtubs should be avoided; only showers should be taken. Activities such as climbing of heights, swimming without supervision, driving, contact with heavy machinery and fire, and other activities that could be dangerous in the event of a seizure should be avoided.

C. Parents should guard against overprotection, which can develop out of fear and anxiety. Unnecessary limitations prevent the child from taking the risks necessary for him or her to become an independent person and develop self-confidence.

D. Parents must inform schoolteachers (as well as babysitters) about the child's seizures. This allows teachers to be prepared to deal with seizures in the classroom and the reactions of classmates. Teachers should be expected to provide information about frequency of seizures during school hours, changes in the child's behavior, unexplained changes in school performance, and abnormal behavioral and social problems that may require referral for counseling.

E. If certain activities must be restricted because of poor seizure control, substitute exercise programs must be found.

F. A medication schedule that avoids school hours should be planned because it often is inconvenient and embarrassing for a child to take AEDs at school.

G. Children with epilepsy have an increased risk of learning disabilities, attention deficit hyperactivity disorder, anxiety and depression. The Food and Drug Administration (FDA) has warned that AEDs may be associated with suicidal ideation.

H. Referral to services such as the Epilepsy Foundation of America or local support groups for counseling.

Status Epilepticus

I. DEFINITION

One or more seizures lasting for more than 30 minutes without full recovery of consciousness between seizures.

II. TYPES

A. Generalized convulsive status epilepticus is characterized by persistent GTCS. In children, it is associated with a higher morbidity and mortality than in adults. We therefore focus on the management of this type of status epilepticus.

B. Nonconvulsive status epilepticus includes cases of absence status and complex partial status and often is described as "twilight state."

III. PRECIPITATING FACTORS

A. Abrupt discontinuation, noncompliance, or changes in anticonvulsant therapy.
B. Acute intercurrent infections such as meningitis and encephalitis.
C. Acute metabolic disturbances, such as electrolyte disturbances, hypoglycemia.
D. Acute cerebral insult such as anoxia, hypoxia–ischemia, trauma (SAH, subdural hematoma, and depressed skull fractures).

IV. PROGNOSIS

Approximately 15% of all patients with epilepsy have an episode of status epilepticus at some time in their lives. Morbidity is higher among children than among adults (approximately 10% to 25%), including most commonly hemiplegia and mental retardation. Recurrent status epilepticus is more common among children.

V. TREATMENT

A. Confirmation of diagnosis of status epilepticus. The longer the seizure continues, the more difficult it is to control and the greater the possibility of permanent brain damage.

B. General measures

1. Initiate supportive measures—see Table 38.4.
2. Place an IV line (preferably two, one with normal saline solution). Blood should be obtained at this time for CBC, electrolytes, calcium, magnesium, glucose, liver function tests, AED levels, toxicology screening, and blood cultures.
3. Administer IV 50% glucose at 2 ml per kg.
4. Identify and treat precipitating factors. For a patient with known seizures in whom status epilepticus may have been caused by AED withdrawal, the treatment of choice is reinstatement of the same drug.

C. Drug treatment involves administration of a drug for immediate termination of the seizure and a second drug for maintenance therapy. The initial treatment is similar regardless of the type of seizure. Maintenance treatment varies depending on the type of epilepsy. The protocol is presented in Table 38.4.

1. **Benzodiazepines.**
   a. **Lorazepam (Ativan; Wyeth-Ayerst)** is recommended as a first-line treatment. The advantages are rapid onset of action, prolonged antiepileptic activity compared with diazepam, and less respiratory depression after previous administration of anticonvulsants such as phenobarbital.
   b. **IV diazepam** (0.2 to 0.5 mg/kg/dose, maximum of 5 mg administered over 2 to 5 minutes) also can be used. The disadvantages include short duration of action

TABLE 38.4 Management of Generalized Tonic–Clonic Status Epilepticus in Children

Time from Start of Treatment	Procedure
0 min	Verify diagnosis of status epilepticus. Monitor cardiorespiratory function. Administer oxygen by nasal cannula or mask, obtain vital signs, ECG, pulse oximetry, insert IV line. Draw, glucose, electrolytes, calcium, magnesium, BUN, CBC, and AED levels if applicable. Start IV normal saline solution. Administer 50% glucose at 2 ml/kg
5 min	IV lorazepam, 0.05–0.1 mg/kg, at 1–2 mg/min to maximum of 5 mg, may be repeated in 10 min if needed. 10–30 min. If seizures continue, start IV fosphenytoin 20 mg PE/kg infused at 3 mg PE/kg/min, not to exceed 150 mg PE/min (if not available, use IV phenytoin 20 mg/kg, at 1 mg/kg/min, not to exceed 50 mg/min) with ECG and blood pressure monitoring; additional 10 mg/kg may be given if seizures continue
31–60 min	If seizures persist, administer IV phenobarbital 20 mg/kg at a rate of 1 mg/kg/min, not to exceed 50 mg/min; additional 10–20 mg/kg may be given if seizures continue
>60 min	If seizures persist, options include: (1) IV pentobarbital—initial loading dose of 5 mg/kg followed by maintenance infusion of 1–3 mg/kg/hr with EEG monitoring to produce burst-suppression pattern. (2) IV diazepam—continuous infusion, 50 mg diluted in 250 ml normal saline or D5W at 1 ml/kg/hr (2 mg/kg/hr) to achieve blood levels of 0.2–8 mg/ml. (3) IV Midazolam 0.1–0.3 mg/kg loading dose followed by maintenance infusion of 0.05–2 mg/kg/hr. (4) Propafol 1–2 mg/kg loading dose followed by maintenance infusion of 1–10 mg/kg/hr. If seizures are not controlled, ask an anesthesiologist to institute general anesthesia with halothane and neuromuscular blockade

Abbreviation: D5W, 5% dextrose in water.

(<30 minutes), high incidence of respiratory depression, and tendency to precipitate tonic status in patients with LGS.

2. **Fosphenytoin (Cerebyx; Parke-Davis).** After IV lorazepam has been administered, IV fosphenytoin is given to achieve therapeutic levels of 18 to 20 μg per ml. Fosphenytoin is a water-soluble disodium ester prescribed as equimolar amounts of phenytoin called *PEs*. This prodrug is rapidly converted to phenytoin by phosphatase in the blood stream, reaching peak brain levels 15 minutes after administration. The loading and maintenance doses of fosphenytoin in PEs are identical to those of phenytoin. Fosphenytoin can be administered IV and intramuscularly with minimal local tissue damage and at faster rates of administration with fewer adverse effects than with phenytoin. Pruritus and paresthesia can occur. IV phenytoin can also be used. Disadvantages of phenytoin include cardiac arrhythmias and hypotension requiring close electrocardiographic and blood pressure monitoring. Intramuscular administration is avoided because of unpredictable absorption and muscle irritation. IV extravasation can result in phlebitis and tissue necrosis. Poor absorption occurs in children, resulting in difficulty in maintaining steady therapeutic levels, especially when the patient is switched to the oral form for maintenance. Phenytoin should be administered in normal saline solution, because it precipitates in glucose solutions.
3. **IV phenobarbital** is administered if seizures persist. It is often used as the first choice in children under 6 years of age. In the treatment of neonates, this may be administered as a single dose. In the case of older children, it may be divided into aliquots of 10 mg per kg to avoid respiratory depression until seizures stop or a maximum loading dose of 20 mg per kg. Additional 10 to 20 mg per kg may be necessary to achieve therapeutic levels of 35 to 40 μg per ml. Disadvantages of phenobarbital include hypotension and respiratory depression.
4. **A more detailed history interview and neurologic examination** should be performed at this time. Evaluate the initial blood work. Before initiating additional therapies, it is preferable to obtain CT scans without contrast enhancement and to perform LP to look

for causes such as intracranial structural lesions or infections. Consider LP for any child with a fever, especially if younger than 18 months, because meningitis can occur without clinical signs of neck stiffness.

5. **Refractory status epilepticus.** If seizures persist for 60 minutes and the patient does not respond to loading doses of fosphenytoin and phenobarbital, anesthetizing agents such as pentobarbital, midazolam, propafol, or diazepam should be considered. Phenobarbital can be used in additional IV boluses of 5 to 10 mg per kg with EEG monitoring until seizures stop and a burst-suppression pattern is obtained on the EEG. The disadvantage of phenobarbital coma is that because of a longer half-life, the effect takes longer to wear off.

   The recommended duration of pharmacologic induced coma is 48 to 72 hours. During this time, the patient is rechecked for seizures by means of decreasing the infusion rate. If seizures persist, the procedure is repeated. If seizures are adequately controlled, medication is slowly withdrawn. Administration of coma requires an intensive care unit setting with controlled mechanical ventilation and close cardiac monitoring.
6. If seizures are still not controlled, general anesthesia with halothane and neuromuscular blockade is recommended.

Medication Withdrawal

Although there is no consensus on how long a patient should remain seizure-free before drug withdrawal is considered, a seizure-free period of 2 to 4 years is recommended. Relapse rates are higher among adults than among children. Approximately 50% of seizure recurrences occur within 6 months of tapering the AED, and 60% to 90% occur within the first year. Children with febrile seizures have a 97% chance of outgrowing them by 6 years of age. There is an 80% to 85% chance of remission among children with absence seizures.

I. FAVORABLE FACTORS ASSOCIATED WITH LOWER RELAPSE RATE

- **A.** Reasonable ease of seizure control.
- **B.** Normal neurologic examination findings and developmental milestones.
- **C.** Normal EEG findings at time of withdrawal.
- **D.** Seizure onset between 2 and 12 years of age.
- **E.** Certain seizure types—febrile seizures, BCECTS, absence seizures.

II. UNFAVORABLE FACTORS ASSOCIATED WITH INCREASED CHANCE OF RECURRENCE

- **A.** Seizures of long duration before successful establishment of control.
- **B.** Abnormal EEG findings at time of medication withdrawal.
- **C.** Abnormal neurologic examination findings.
- **D.** Seizure onset <2 years of age or after 12 years of age.
- **E.** Certain seizure types—focal seizures, infantile spasms, LGS.

Vagal Nerve Stimulation

In the United States, FDA approval indicates use of vagal nerve stimulation as adjunctive therapy for refractory partial seizures in the care of adults and children older than 12 years. It has also successfully been used in younger children for other seizure disorders such as LGS. Indications for consideration of the device include medically refractory seizures, adequate trial of at least three AEDs, exclusion of nonepileptic events, and lack of surgery

candidacy. Children who have undergone vagotomy (unilateral or bilateral) should not be given implants. Cervical masses should be excluded because cervical MRI may not be performed once the device is implanted. Cardiac arrhythmias, conduction abnormalities, and chronic obstructive pulmonary diseases also are considered as risk factors. Common side effects include voice hoarseness, cough, dyspnea, and rarely left vocal cord paralysis and parasthesias.

Surgical Therapies

Procedures that resect or disconnect epileptogenic areas can reduce or eliminate seizures in patients with medically intractable epilepsy. These procedures are performed in specialized epilepsy centers. Extensive preoperative evaluation includes video EEG monitoring to identify seizure focus, neuropsychiatric evaluation, neuroimaging studies (MRI, SPECT, and PET), intracarotid amobarbital test (Wada's test), and even invasive studies (subdural and depth electrodes), if indicated. The most common types of epilepsy surgery in the care of children are as follows.

I. RESECTIVE SURGERY

Removal of the epileptogenic area (e.g., temporal lobectomy).

II. CORPUS CALLOSOTOMY

Interruption of the anterior two-thirds of the corpus callosum, effective for atonic seizures, tonic seizures, and GTCS.

III. HEMISPHERECTOMY

One cerebral hemisphere is disconnected from the rest of the brain, and a limited area is resected. It is performed for early-onset or congenital hemiplegia in which seizures arise from one side of the brain.

Recommended Readings

Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389–399.

Pellock JM, Bourgeois BFD, Dodson WE, eds. *Pediatric Epilepsy: Diagnosis and Therapy*. 3rd ed. New York, NY: Demos; 2008.

Roger J, Bureau M, Dravet C, et al., eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. 4th ed. France John Libbey Eurotext; 2005.

Wyllie E, Cascino GD, Gidal BE, et al. *Wyllie's Treatment of Epilepsy: Principles and Practice*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

CHAPTER

39 Epilepsy in Adults

Omkar N. Markand

I. DEFINITIONS

A. An epileptic seizure is a transient and reversible alteration of behavior caused by a paroxysmal, abnormal, and excessive neuronal discharge.

B. Epilepsy usually is defined as two or more recurring seizures not directly provoked by intracranial infection, drug withdrawal, acute metabolic changes, or fever.

II. CLASSIFICATIONS

There are two classifications—one of seizure types and one of epilepsy or epileptic syndromes. Accurate diagnosis of the type of epileptic seizure and the categorization of epilepsy (or epileptic syndrome) for each patient are essential for proper selection of antiepileptic drug (AED) therapy and for prognosis.

A. Classification of epileptic seizures is based on the patient's behavior during seizures and on the associated EEG characteristics. Epileptic seizures are classified into two main types—partial and generalized.

1. **Partial (focal) seizures** arise at specific loci in the cerebral cortex and are associated with focal interictal and ictal EEG changes. Clinically, a partial seizure can range in intensity from a disorder of sensation without loss of consciousness to a generalized convulsion.
   a. **Simple partial seizures.** Consciousness remains intact. Such seizures can be motor seizures (focal motor twitching or Jacksonian seizures), sensory seizures (numbness or tingling involving parts of the body), autonomic seizures, or seizures with psychic symptoms.
   b. **Complex partial seizures.** Consciousness is impaired during complex partial seizures. Previously, these seizures were called *psychomotor seizures.* They constitute the most common type of seizure in adults. Approximately 85% have an epileptogenic focus in the temporal lobe, whereas the remaining 15% are of extratemporal origin, usually frontal.
   c. **Secondarily generalized (tonic–clonic) seizures.** During any focal seizure (simple or complex partial), the epileptic excitation can spread widely to the entire brain, resulting in a generalized tonic–clonic convulsion.
2. **Generalized seizures** are characterized by generalized involvement of the brain from the outset and have no consistent focal areas of ictal onset. There are many subtypes.
   a. **Absence seizures** were formerly known as *petit mal seizures.* The dominant feature is a brief loss of consciousness with no or minimal motor manifestations (e.g., twitching of the eyelids). During the seizure, EEG shows 3-Hz generalized spike–wave discharges.
   b. **Myoclonic seizures** are brief jerks involving part of the body or the entire body.
   c. **Clonic seizures** are rhythmic twitching of the body.
   d. **Tonic seizures** are brief attacks of stiffness in part of the body or the entire body.
   e. **Atonic seizures** are losses of posture with resultant drop attacks.
   f. **Tonic–clonic seizures** are generalized convulsions or grand mal seizures. It is important to emphasize that some tonic–clonic (grand mal) seizures are generalized from the outset and some are secondarily generalized (they start as focal seizures and then become generalized). The second type is the most common among adults. The presence of an aura, focal manifestations during the seizure, and postictal focal deficits favor a secondarily generalized tonic–clonic seizure.

Confusion can arise in differentiating absence seizures and complex partial seizures. Both can present with a brief loss of awareness or altered responsiveness, and in both there may be automatic activities of various kinds. Diagnosis is aided by EEG findings (generalized spike–wave discharges in absence seizures and focal epileptiform abnormalities in complex partial seizures). Correct diagnosis is critical for instituting proper AED therapy.

B. Classification of epilepsy or epileptic syndromes. Classifying the seizure type, although useful, is of limited value because seizures usually appear as part of a cluster of other symptoms and signs that include etiologic factor, site of seizure onset, age, precipitating factors, response to medication, and prognosis. Hence, the ultimate goal is to diagnose epilepsy or an epileptic syndrome. This is very important. It helps to choose the appropriate AEDs to control seizures and to avoid using an AED, which may not only be ineffective but may even exacerbate seizures.

1. **Localization-related (focal or partial) epilepsy or epileptic syndromes** are disorders in which a localized origin of the seizures can be established. The patient has focal or secondarily generalized tonic–clonic seizures. EEG shows focal epileptiform discharges overlying the epileptogenic focus.
   a. Most localization-related forms of epilepsy are **acquired** or **symptomatic.** Temporal lobe epilepsy is the common localization-related epilepsy among adults, and it is often associated with mesial temporal sclerosis on the MRI scan.
   b. There are age-related **idiopathic** or **primary** localization-related epileptic syndromes. The best known is benign rolandic epilepsy of childhood.
2. **Generalized epilepsy or epileptic syndromes** are disorders that involve one or more types of generalized seizures. EEG shows generalized epileptiform abnormalities.
   a. **Primary (idiopathic) generalized epilepsy (PGE)** is characterized by generalized seizures without any identifiable etiologic factor. EEG shows generalized spike–wave or polyspike–wave discharges with a normal background activity. Genetic factors predominate in these forms of epilepsy. Common syndromes include childhood absence epilepsy, juvenile myoclonic epilepsy, juvenile absence epilepsy, and tonic–clonic seizures occurring often in the early morning ("awakening" grand mal).
   b. **Secondarily (symptomatic) generalized epilepsy** is characterized by various types of generalized seizures resulting from acquired cerebral diseases (e.g., seizures secondary to ischemic–hypoxic encephalopathy or following severe cerebral trauma or intracranial infection) or from inborn errors of metabolism (e.g., lipidosis and progressive myoclonus epilepsy). EEG shows generalized, irregular spike–wave, 2.5 Hz in frequency with an abnormally slow background activity. Patients usually have varying degrees of cognitive and neurologic deficits, and the seizures are often drug resistant. Within this category are two commonly recognized age-related syndromes—**West's syndrome** (infancy) and **Lennox–Gastaut's syndrome** (childhood).

III. EVALUATION

It is essential to establish that the spells or episodes are indeed epileptic seizures. Nonepileptic physiologic disorders that result in transient, reversible alterations of behavior or function, such as syncope, migraine, breath-holding spells, anxiety episodes, transient ischemic attacks, hypoglycemic episodes, and narcoleptic–cataplectic attacks, must be differentiated from epileptic seizures. Moreover, there are nonepileptic psychogenic seizures or pseudoseizures that are conversion reactions characterized by episodes of motor activity and loss of consciousness but not associated with ictal EEG patterns and without an underlying physiologic basis.

A. A **history** of the episodes, obtained not only from the patient but also from one or more observers, is perhaps the most essential element in making the diagnosis of epileptic seizures and differentiating them from nonepileptic disorders. The history can aid in ascertaining the type of epileptic seizures.

B. Physical and neurologic examinations can help detect the underlying cause of the brain disorder responsible for the epilepsy by uncovering evidence of a focal cerebral lesion or another organic disorder, such as tuberous sclerosis or neurofibromatosis.

C. Neuroimaging. Although CT of the head with and without contrast enhancement is performed on most patients believed to have epilepsy, MRI of the head is the imaging procedure of choice. MRI is particularly sensitive in detecting hamartoma, cavernous malformation, and low-grade glioma and in providing evidence of mesial temporal sclerosis in patients with temporal lobe epilepsy.

D. EEG is the most informative test for confirmation of the diagnosis of epilepsy and proper classification of the seizure type and even the epileptic syndrome. It also aids in initiation, selection, and discontinuation of antiepileptic therapy (see Chapter 33).

Not all patients with epilepsy have interictal epileptiform abnormalities; approximately 50% have such abnormalities in a routine awake-and-asleep EEG study that includes hyperventilation and intermittent photic stimulation. The yield increases with repeated EEG studies with sleep deprivation and extra recording electrodes. On the other hand, 1% to 2% of healthy persons without clinical seizures have epileptiform abnormalities in EEG studies. Hence, an interictal EEG alone can neither prove nor exclude a diagnosis of epilepsy. Similarly, the presence of interictal epileptiform EEG abnormalities does not automatically warrant AED therapy, and the absence of such abnormalities is not sufficient grounds for discontinuing AED treatment.

E. Intensive video EEG monitoring. Patients with drug-resistant epilepsy or poorly characterized episodes may need intensive monitoring that consists of simultaneous monitoring of the patient's behavior and EEG to provide detailed clinical and EEG correlation of episodic events. This is an expensive and time-consuming technique and thus is left to the discretion of a consulting neurologist specialized in epilepsy. Only 5% to 10% of patients believed to have epilepsy need this technique to characterize and classify the epileptic episodes. Video EEG is mandatory in the presurgical evaluation of patients to document epileptic seizures prior to surgical resection to treat epilepsy, and even before placing a patient on vagal nerve stimulation (VNS). It is most helpful in patients who have frequent episodes that are suspected to be of the nonepileptic type. These episodes are not accompanied by the characteristic ictal pattern in the simultaneously recorded EEG.

IV. GENERAL PRINCIPLES IN TREATING PATIENTS WITH EPILEPSY

A. AED therapy should be initiated only when the diagnosis of epileptic seizures is well-established. If the patient's episodes are yet to be clearly defined and there is reasonable doubt of their being epileptic in nature, it is prudent to wait until the diagnosis of epilepsy can be confirmed.

B. First seizure. AED therapy usually is not initiated after the first tonic–clonic seizure and postponed until a second seizure occurs when the diagnosis of recurrent seizures or epilepsy is made. The incidence of recurrence is 25% to 65% after the first and over 75% after the second seizure. The first seizure can be an isolated episode and not necessarily the onset of epilepsy. This is particularly true if a single tonic–clonic seizure was related to sleep deprivation, physical or mental stress, drug or alcohol withdrawal, or use of prescribed (e.g., Welbutrin) or recreational drugs (e.g., cocaine). In general, 50% of patients have recurrence over a 3-year follow-up period after the first tonic–clonic seizure. The incidence is <25% among subjects with low-risk factors to 65% or more for those with two or more of the following risk factors: strong family history of seizures in siblings, history of febrile convulsions, focal-onset seizure, postictal paralysis, abnormal findings at cognitive and neurologic examinations, evidence of a structural cerebral lesion at neuroimaging, and the presence of epileptiform abnormalities at EEG. Patients with two or more of these risk factors therefore may need prompt initiation of therapy even after the first tonic–clonic seizure.

C. Monotherapy is preferable to the use of several drugs because it has fewer toxic side effects, less likelihood of drug interactions, and better compliance. The chosen AED (Table 39.1) should be slowly increased until seizures are controlled or until clinical signs of toxicity develop. If seizures are not adequately controlled at the maximum tolerable dosage, a second AED is slowly introduced. After the second drug attains therapeutic

TABLE 39.1 AEDs of Choice for Specific Type of Seizures and Epilepsy Syndromes

Type of Seizure or Syndrome	Recommended AED		
	First Choice	Second Choice	Possibly Useful
Partial (focal) epilepsy			
Simple partial, complex partial; secondary generalized tonic–clonic seizures	OXC/CBZ/PHT	TPM/LTG/LTC/PGL/VPA/ZNS/LCM	GBP/PB/PRM/TGB
Primary generalized epilepsy			
Primary generalized tonic–clonic seizures	VPA	TPM/LTG[a]	LTC/ZNS
Absence epilepsy without motor seizures	ESM	VPA/LTG[a]	CLZ
Absence epilepsy with generalized tonic–clonic seizures	VPA	LTG[a]/TPM/LTC	CLZ
Myoclonic seizures	VPA	LTG[a]/LTC/ZNS[b]	CLZ
Myoclonic seizures with absence or generalized tonic–clonic seizures	VPA	LTG[a]/TPM/LTC/ZNS	
Secondary generalized epilepsy			
Usually multiple seizure types, e.g., tonic, absence, myoclonic, clonic, atonic, tonic–clonic	VPA	LTG/TPM/LTC/ZNS/RFM	FBM[c], PHT/CBZ/OXC, ketogenic diet

AEDs separated by virgules are roughly equal in efficacy. The choice of specific AED for a given patient should be based on factors such as toxicity and cost. Sedative AEDs are generally considered second-line drugs.

[a]Because of the risk of neural tube defect with VPA, LTG may be the drug of first choice in treatment of women considering pregnancy.

[b]Particularly useful for progressive myoclonic epilepsy.

[c]High incidence of serious side effects.

Abbreviations: CBZ, carbamazepine; OXC, oxcarbazepine; PHT, phenytoin; TPM, topiramate; LTG, lamotrigine; LTC, levetiracetam; VPA, valproic acid; ZNS, zonisamide; GBP, gabapentin; PB, phenobarbital; PRM, primidone; TGB, tiagabine; ESM, ethosuximide; CLZ, clonazepam; FBM, felbamate; PGL, pregabalin; LCM, lacosamide; RFM, rufinamide.

levels, the first drug is gradually withdrawn. Monotherapy adequately controls new-onset epilepsy in about two-thirds of the patients.

D. **Polytherapy** with a combination of two AEDs (usually one traditional and one newer AED) becomes necessary only if monotherapy with two or more first-line AEDs has been unsuccessful. When using two AEDs, select those with different mechanism of action. Avoid using more than two AEDs simultaneously. If a combination of two AEDs in the treatment of a compliant patient with blood levels in the therapeutic range fails to provide adequate control of epileptic seizures, **referral to an epileptologist or epilepsy center** is indicated for further evaluation and management. After two appropriate AEDs fail to control seizures, monotherapy with a third AED or polytherapy is successful in only 4% of the patients.

E. **AEDs with sedative or hypnotic side effects** need to be avoided unless first-choice AED does not work. Drugs with these effects include phenobarbital, primidone, and clonazepam. Often a patient undergoing polytherapy that includes one of the aforementioned sedative AEDs is best served by very gradual withdrawal of the sedative AED while the dosage of the other AED is maximized. Discontinuation of sedative–hypnotic AEDs is followed not only by a reduction in side effects but also by better control of seizures in many instances.

F. **Simplify drug schedules.** Most AEDs have long elimination half-lives (see Tables 39.3 and 39.5), and thus can be prescribed in a single daily dose or two divided daily doses. Exceptions include the traditional AEDs, such as valproic acid and carbamazepine (extended release valproate and sustained release carbamazepine are now available), and the new AEDs such as gabapentin and tiagabine, which have to be given in two or three divided daily doses. With multiple AEDs, half-lives of some AEDs are shorter than when the same drug is given in monotherapy. Thus, larger doses and multiple dosing are required.

G. **Compliance** must be emphasized. Medication is best taken at the time of meals for easy remembrance. For most AEDs, an occasional missed dose can be made up by taking an additional dose within the same 24-hour period. It is also convenient for the patient to put the medication in a plastic pillbox with divided compartments and to ensure at bedtime that the entire day's medication has been taken.

H. Advise the patient to maintain a **seizure diary.** Such a diary provides an accurate record of the frequency of seizures and assists in evaluating the effectiveness of the therapy.

I. Emphasize to the patient the need for constant **medical follow-up care.** Once AED therapy is well-established and the seizures have been brought under satisfactory control, the patient should be examined every 6 to 12 months. During the follow-up visits, evaluate the patient for evidence of drug toxicity or development of a progressive neurologic disorder. CBC, liver function tests, and serum electrolytes may need to be performed every 6 to 12 months to detect untoward effects of AEDs on the bone marrow and liver. However, routine blood testing at periodic intervals is a controversial issue because serious side effects are rare and, when they occur, they do so over a short period to be detected by periodic monitoring.

J. A patient who achieves good control with drug therapy may have a **"breakthrough" seizure** during periods of physical or mental stress, sleep deprivation, or infection. Appropriate management of such precipitants rather than increases in dose or changes in the AED is indicated.

K. **Generic substitution** for brand-name AEDs can reduce the cost of medication, but the bioavailabilities of generic and proprietary AEDs are not the same. Generic preparations are required by the U.S. Food and Drug Administration (FDA) to provide bioavailabilities within ±20% of those of the corresponding proprietary formulations, but some patients may be sufficiently sensitive to these fluctuations that replacing one with the other leads to either loss of seizure control or signs of neurotoxicity. This problem applies primarily to phenytoin and carbamazepine. The proprietary phenytoin (Dilantin; Pfizer, New York, NY, USA) is more slowly absorbed than is generic phenytoin, so blood levels are maintained with less fluctuation, and no more than one or two daily doses are required. Similarly, brand-name carbamazepine (Tegretol; Novartis, East Hanover, NJ, USA) is absorbed more slowly than is the generic formulation. It is probably prudent to continue name brand AED if the patient is seizure free on

that formulation. If changed to generic AED the patient needs to be warned of the possibility of break-through seizures or drug toxicity. The patient should avoid switching between formulations of AEDs. When a generic AED is used, the formulation by the same manufacturer should be refilled.

L. **Therapeutic drug levels** are rough guides to the ranges that in most patients provide best seizure control while avoiding dose-related side effects. The blood should be drawn preferably before the morning dose of AEDs so as to obtain the lowest (trough) levels. The blood levels are not to be followed rigidly for a given patient. Some patients may attain complete seizure control at low "therapeutic" levels, and increasing the dose to attain idealized levels is not indicated. On the other hand, there are patients who need higher than "therapeutic" levels for control of their seizures and tolerate such levels without significant untoward side effects. In such patients, it is fully justified to maintain phenytoin level as high as 20 to 30 μg per ml, valproic acid level as high as 100 to 150 μg per ml, and carbamazepine level as high as 12 to 15 μg per ml. Anticonvulsant blood levels are indicated under the following circumstances:

1. To determine the baseline plasma dose level.
2. When the patient is believed to be noncompliant.
3. When the patient does not respond adequately to the usual dosage of an AED.
4. When symptoms and signs of clinical toxicity are suspected.
5. When there is a question of drug interaction.
6. To establish the correct dosage for a pregnant patient or a patient with diseases affecting the pharmacokinetics of the AEDs (hepatic, renal, or gastrointestinal disorders).

Total serum levels of AEDs usually are obtained. When metabolism of AEDs may be altered or serum protein levels are likely to be low (e.g., hepatic or renal disorders and pregnancy), free levels of highly protein-bound AEDs may become necessary.

M. Emphasize the need to regularize the time and duration of sleep, because **sleep deprivation** tends to potentiate seizures.

N. **Concomitant use of other drugs.** Alcohol in any form is best avoided or used in small amounts (e.g., one drink) because of possible interactions with most AEDs. Be aware of drugs that lower the seizure threshold (e.g., tricyclic antidepressants, Welbutrin, and phenothiazines) or those that can cause drug interactions (increasing or decreasing the levels of AEDs); they should be used with caution. Some AEDs affect the elimination kinetics of many drugs metabolized in the liver (e.g., birth control pills, corticosteroids, anticoagulants, and cyclosporine), necessitating proper dose adjustment of these comedications.

O. Encourage the patient to make the adjustments necessary for leading a normal life as much as possible. Moderate exercise does not affect seizure frequency. Encourage a regular exercise program. Participation in highly competitive sports increases the risk of physical injury. Individualize instructions to the patient by considering the risk of a particular sport against the patient's needs. Swimming may be permitted under supervision for a patient with good control of seizures. Bathing in a bathtub is to be avoided; taking a shower is recommended instead.

P. Most adults who have epilepsy are able to maintain competitive **employment** and should be encouraged to do so. This improves their self-esteem and their acceptance in the mainstream of society. There are, however, some realistic limitations on the types of work a patient with epilepsy can be permitted to do. Certain occupations, such as working with heavy machines, working above ground level, working close to water or fire, driving trucks or buses, and flying planes, may be off limits for reasons of personal and public safety. There are still scores of jobs such as secretary, lawyer, physician, accountant, and stockbroker that are acceptable.

Q. Family members or caregivers should be educated regarding proper care of the patient when a seizure occurs. During a grand mal seizure, the patient should be helped to lie on the ground, a bed, or a couch and should be turned on one side to avoid aspiration. An object such as a spoon or a finger should *never be thrust into the patient's mouth*. It is a myth that the tongue can be swallowed during a seizure. Pushing a hard object into the mouth often results in broken teeth. The patient must be closely watched and the sequence of events observed during the seizure, which can help determine the type of seizure.

R. For a patient with a known history of seizures, an isolated self-limiting seizure does not constitute a need to call for an ambulance and have the patient rushed to an emergency department. However, if the seizure lasts longer than 5 minutes or if the patient has repeated seizures without regaining consciousness between them, prompt transfer to a nearby hospital becomes essential. Prompt medical attention must also be sought if patient had a fall and sustained bodily injury.

S. Driving. Most states have laws denying driving privileges to patients with uncontrolled epilepsy but permit driving once the seizures have been brought under control with AEDs. In a few states, doctors are required to report cases of epilepsy. The period of time that the patient must remain seizure-free before being permitted to drive varies from 3 months to 2 years, depending on the state. Rare patients who have only nocturnal seizures or who have only simple partial seizures (no loss of consciousness) may be exempted from driving restrictions. Reinstitution of driving privileges may require reapplication, a letter from the treating physician, or a determination made by a state-appointed board. Some states require the treating physician to certify at regular intervals that the patient has continued to remain seizure-free before reissuing the driving permit. Because the laws regarding driving vary widely among different states and are frequently changing, physicians are best advised to obtain their current state registration.

In general, patients with frequent seizures with altered consciousness must be advised to refrain from driving until seizures can be satisfactorily controlled. That the patient has been properly advised must be documented in the patient's record.

There is no consensus as to how long the patient should be advised not to drive after having a breakthrough seizure after a long seizure-free period. If such a seizure follows a known precipitant such as infection, mental or physical stress, prolonged sleep deprivation, or poor compliance, observation for at least 3 to 6 months is required before driving is again permitted.

V. SELECTION OF AED

Table 39.1 lists AEDs effective for managing various forms of epilepsy and epileptic syndromes.

A. Symptomatic partial (localization-related) epilepsy. Several well-designed studies have shown that for simple partial, complex partial, and secondarily generalized tonic–clonic seizures, several AEDs, including phenytoin, carbamazepine, valproate, phenobarbital, and primidone, have similar antiepileptic efficacy but differ greatly in toxicity. Primidone and phenobarbital are more often associated with neurotoxicity, probably less effective against simple and complex partial seizures, hence, usually avoided. Valproate is somewhat less effective against complex partial seizures than carbamazepine. There are very small differences in overall effectiveness and basic mechanism of action between carbamazepine and phenytoin. Hence, **carbamazepine** and **phenytoin** can be considered as the first-line "traditional" AEDs.

Phenytoin is relatively inexpensive, which can be titrated rapidly in 2 to 3 days, is better tolerated in the initial period of therapy, and can be given in one to two divided daily doses. However, it has a high incidence of chronic dysmorphic side effects, such as hirsutism, coarsening of facial features, and acneiform eruptions, which makes its use rather unacceptable in women. Its nonlinear kinetics makes the dose adjustment difficult during maintenance therapy. **Carbamazepine** has no dysmorphic effects and hence is better accepted by adolescent and young adult female patients. Its short half-life usually necessitates using it in three or four divided doses, but sustained-release preparations are now available and given in two daily doses. It needs to be slowly titrated over 3- to 4-week period due to autoinduction. Cognitive side effects with long-term use of phenytoin or carbamazepine have been found to be equally frequent in recent studies and both require periodic blood monitoring for bone marrow and liver functions. **Oxcarbazepine,** which has lesser side effects, rapid titration, and no requirement for blood monitoring, is emerging as a more favored newer AED alternative to carbamazepine since its approval by the FDA for monotherapy in adults with focal epilepsy.

Most physicians now recommend using oxcarbazepine or carbamazepine be used initially as monotherapy. If one of the two is ineffective, it can be replaced with the other. If monotherapy with carbamazepine or oxcarbazepine fails to achieve satisfactory control, a combination therapy with valproic acid is tried—carbamazepine plus valproic acid, or oxcarbazepine with valproic acid. Alternatively, adjunctive therapy with newer AEDs should be strongly considered by adding levetiracetam, lamotrigine, topiramate, zonisamide or lacosamide to carbamazepine, or oxcarbazepine, based on the lesser risk of toxicity and drug interaction of these newer AEDs. Combination therapy is more likely to produce cognitive and other side effects.

Even with adequate AED therapy, only 40% to 60% of patients with symptomatic partial epilepsy, particularly those with complex partial seizures (the most common type of seizures among adults) attain full control of seizures. In one study of new onset epileptic seizures, initial monotherapy was effective in 47% of patients. Changing to a second drug controlled another 13% of patients. Use of a third AED or combined therapy with two or more AEDs controlled only 4% of additional patients. Most experts believe that, if an adequate trial with two or three AEDs (including at least one newer AED) either as monotherapy or combined therapy fails, the patient has **medically refractory epilepsy.** Such a patient will need a referral to a comprehensive epilepsy center for further management.

B. Primary (idiopathic) generalized epilepsy. Most patients with PGE have either absence, myoclonic, or tonic–clonic seizures, and most have more than one type of seizure, although one type may dominate. Depending on seizure type, several epileptic syndromes are identified under the heading PGE. The best example is juvenile myoclonic epilepsy, which is characterized by myoclonic seizures in the early hours after waking, but most patients also have occasional tonic–clonic seizures. Less often, even absence seizures may occur. Other syndromes include primary tonic–clonic seizures (contrasted to secondarily generalized tonic–clonic seizures, which are part of focal epilepsy), which commonly occur in the morning hours and hence are called "awakening" grand mal seizures. Absence seizures as the dominant manifestation of PGE commonly occur in childhood (childhood absence epilepsy), but in rare cases start in adolescence or early adulthood (juvenile absence epilepsy).

1. For **absences,** both ethosuximide and valproic acid are equal and very effective in controlling these seizures in over 80% of patients. Patients with childhood or juvenile absence epilepsy who have absence seizures only can, therefore, be treated with either ethosuximide or valproic acid. **Ethosuximide** is preferred because of its lesser toxicity and longer half-life allowing it to be taken in only one or two divided daily doses. But those patients who have additional myoclonic and/or tonic–clonic seizures do need valproic acid for treatment of both absence and motor seizures because ethosuximide is ineffective against motor events.
2. **Valproic acid** has clearly been the drug of choice for PGE where **multiple seizure types** are likely to be present, including the syndrome of juvenile myoclonic epilepsy, primary grand mal seizures, or combined absence–grand mal epilepsy. The advantage of valproic acid is that it is effective against all seizure types comprising PGE.
3. Appropriate AED therapy is very effective, and good seizure control is possible for as many as 80% to 90% of patients with PGE.
4. **Clonazepam** is an effective AED for myoclonic and absence seizures but has certain disadvantages. It has a high incidence of sedative and cognitive side effects, and patients develop a tolerance to its antiepileptic potency after several months of therapy. Furthermore, its use may start or exacerbate tonic–clonic seizures in juvenile myoclonic epilepsy. Use of clonazepam has, therefore, declined since the introduction of newer AEDs. If used for myoclonic or absence seizures, clonazepam can be added to valproic acid if the latter by itself fails to be fully effective.
5. Because of the high incidence of fetal malformations, polycystic ovarian syndrome (PCOS), and weight gain, the use of valproic acid in women with PGE needs to be restricted because recent well-designed studies have demonstrated effectiveness of the **newer AEDs,** several of which are broad spectrum in their efficacy.

a. **Lamotrigine** is effective against absences, has low teratogenicity, and is a weight neutral AED. It is a good alternative for treating absences associated with childhood and juvenile absence epilepsy. Very recent studies, however, have shown it to be somewhat less effective compared with ethosuximide or valproic acid.
b. **Lamotrigine** is also found to be effective in juvenile myoclonic epilepsy, although it can occasionally exacerbate myoclonic seizures.
c. **Topiramate** is effective in PGE manifesting with generalized tonic–clonic seizures and approved by the FDA for this indication.
d. **Levetiracetam** is effective in all seizure types accompanying PGE and particularly against myoclonic seizures.
e. **Zonisamide** is probably effective, also, against all seizure types of PGE, but has more sedative side-effects than lamotrigine and levetiracetam.

6. Although most patients with PGE can be well-controlled with appropriate AEDs, some 15% are medically refractory. Some are **pseudo-refractory** because they are on wrong AEDs. In recent years, sodium-channel blocking and gamma-aminobutric acid (GABA)-enhancing AEDs have been recognized to exacerbate certain seizure types in patients with PGE. Carbamazepine, oxcarbazepine, phenytoin, vigabatrin, tiagabine, gabapentin, and pregabalin commonly exacerbate absence seizures, myoclonic jerks, or both, and should not be used in the treatment of PGE. It is, therefore, critical that the patient needs to have the syndromic diagnosis of PGE established even though the precise subtype of PGE may not be identified. This will prevent iatrogenic exacerbation of seizures.

In truly refractory cases, **combination therapy** using Depakote with either levetiracetam, lamotrigine (but be aware of markedly decreased elimination of lamotrigine by valproic acid), topiramate, or zonisamide may be more effective. Combination of Depakote and ethosuximide may control absences more effectively than either drug alone.

C. Secondarily (symptomatic) generalized epilepsy, which is secondary to multifocal or diffuse cerebral disorders (static or progressive), occurs mostly among children and less often among adults. Patients have multiple seizure types, including atypical absence seizures, myoclonic seizures, tonic seizures, tonic–clonic seizures, and drop attacks.

In general, response to any AED is poor, only 20% to 40% of patients attaining acceptable seizure control. Such patients commonly end up being treated with polypharmacy, which not only fails to provide better seizure control than do one or two AEDs but may even exacerbate certain types of seizures (absence seizures, myoclonic seizures, and drop attacks).

Valproic acid is the AED of first choice for secondarily generalized epilepsy and may be started as monotherapy. However, most patients need an addition of newer AEDs. Of these, **lamotrigine, topiramate, zonisamide,** and **levetirecetam** have been found useful in clinical trials. **Felbamate** and **rufinamide** have been approved by FDA for the control of seizures associated with secondary generalized epilepsy of the Lennox–Gastaut's type but felbamate has potentially serious hepatic and bone marrow toxicity. When drug combinations are prescribed, appropriate dosages should be used to avoid sedation, which tends to exacerbate minor seizures as well as precipitate statuses in such patients.

VI. TRADITIONAL AEDS

Mechanism of action, indications, and common side effects of traditional AEDs are listed in Table 39.2, and their pharmacokinetic characteristics and adult dosages in Table 39.3.

A. Efficacy. In general, the traditional AEDs have limited efficacy against epileptic seizures especially those associated with focal or partial epilepsy.

1. The first landmark VA study in 1985 compared carbamazepine, phenytoin, primidone, and phenobarbital in the treatment of partial epilepsy. All four of those AEDs were shown to be equally effective as monotherapy for secondarily generalized tonic–clonic seizures, whereas carbamazepine and phenytoin were more effective and better tolerated than primidone and phenobarbital in the treatment of complex partial seizures.

2. The second VA study in 1992 demonstrated that carbamazepine was superior to valproic acid in the treatment of complex partial seizures but both were equivalent for secondarily generalized tonic–clonic seizures.

TABLE 39.2 Mechanism of Action, Indications and Undesirable Side Effects of Traditional AEDs

Medication	Mechanism of Action	Indications	Undesirable Side Effects		
			Weight	OCP	Other Significant
Phenobarbital	↑ GABA ↓ Na	(1) Partial & sec. gen. t–c (mono & adj) (2) GTC status	–	+	Hyperactivity in children, hypersensitivity reaction
Primidone	↑ GABA ↓ Na	Partial & sec. gen. t–c (mono & adj)	–	+	Similar to phenobarbital but more side effects at least initially, erectile dysfunction
Phenytoin	↓ Na	(1) Partial & sec. gen. t–c (mono & adj) (2) PGE with gen. t–c (3) Status epilepticus	–	+	Coarse facies, hirsutism, gum hyperplasia, skin rash, lupus, blood dyscrasia, pseudolymphoma, hepatitis, numerous drug interactions
Carbamazepine	↓ Na	Partial & sec. gen. t–c (mono & adj)	↑	+	Leukopenia, rare severe bone marrow or hepatic toxicity, hyponatremia, serious rash, several drug interactions
Valproic acid	↓ Na ↓ Ca (T) ↑ GABA	(1) Partial & sec. gen. t–c (mono & adj) (2) PGE with absences, myoclonic, t–c szs (3) SGE	↑	–	Hair loss, tremor, hyperammonemia, pancreatitis, thrombocytopenia, hepatic toxicity, PCOS, teratogenicity (spina bifida)
Clonazepam	↑ GABA ↓ Na	(1) PGE with absences, myoclonic or t–c szs (2) Partial epil. with gen. t–c szs	–	–	–
Ethosuximide	↓ Ca (T)	PGE with absences only	–	–	Blood dyscrasias, serious rash

Abbreviations: SGE, secondary generalized epilepsy; Na, sodium currents; Ca (T), low threshold T current; GABA, γ aminobutric acid transmission; OCP, oral contraceptive pill; adj, adjunctive; mono, monotherapy; gen. t–c, generalized tonic–clonic seizures; ↓, decrease; ↑, increase; –, no effect.

TABLE 39.3 Pharmacokinetics and Adult Dosages of Traditional AEDs

AED	Bio-availability (%)	Peak Plasma Level (hr)	Volume of Distribution (L/kg)	Protein Binding (%)	Elimination Half-life (hr)	Time to Steady State (d)	Elimination Route	Starting Adult Dose (mg/d)	Escalation Dose (mg)	Usual Adult Maintenance Dose (mg/d)	Dosing Regimen (times/day)	Therapeutic Level (μg/ml)
Phenytoin	>90	2–12	0.8	90	10–50[a]	7–21	H	300	30–100/4 wk	300–400	1–3	10–20
Carbamazepine	75–85	4–12	0.8	75	10–50[b]	20–30[c] 3–7[d]	H	200	200/wk	600–2,000	3	4–12
Ethosuximide	>90	1–4	0.65	0	30–60	7–14	H 75, R 25	500	250/wk	500–1,500	2	40–100
Valproic acid	>90	1–8	0.2	70–95[e]	5–20	2–5	H	500	250/wk	750–3,000	2, 3	40–120
Phenobarbital	>90	1–4	0.8	40–50	50–120	14–21	H 75, R 25	60	30/4 wk	60–180	1	15–40
Primidone[f]	>90	2–4	0.75	0	6–12	—	H	125	125/3–7 d	750–1,500	3	5–12
Clonazepam	>90	1–4	3.0	85	20–40	7–14	H	1.0	0.5/3–7 d	1.5–10	1–3	0.02–0.08

H, hepatic; R, renal; numbers are approximate percentages for each route.[a]Elimination half-life is concentration dependent; at higher levels the half-life is long.

[b]Elimination half-life is longer in the initial 2–4 wk of therapy before self-induction becomes significant.

[c]Before autoinduction is complete.

[d]After autoinduction is complete.

[e]Concentration dependent, higher binding at low total levels.

[f]Primidone therapy produces three active metabolites: primidone, phenobarbital and phenylethylmalonamide.

3. In both VA cooperative studies, only 25% to 48% patients were seizure-free after 12 months of therapy.
4. Ethosuximide has a narrow spectrum of efficacy, controlling only absence seizures.
5. Valproic acid is the only broad spectrum AED among the traditional drugs, being effective both in partial and generalized epilepsy.

B. Side effects.

1. All traditional AEDs are associated with **neurotoxic side effects** such as tiredness, somnolence, dizziness, ataxia, blurred or double vision, nystagmus, difficulty with concentration, behavioral disturbances, and cognitive dysfunction.
2. Phenobarbital, primidone, and clonazepam have higher incidence of sedative/hypnotic side effects.
3. Paradoxical hyperactivity occurs in children treated with phenobarbital or primidone.
4. Skin rashes have been reported with phenytoin, carbamazepine, ethosuximide, and other AEDs.
5. Phenytoin has several side effects such as coarsening of the facies, facial/body hirsutism in women, and gum hyperplasia. These cosmetic effects are concerning to women.
6. Valproic acid, when used in larger doses, is associated with tremor.
7. Valproic acid and carbamazepine are commonly associated with weight gain.
8. **Serious reactions** to traditional AEDs are reported but are uncommon. These include hepatotoxicity, bone marrow suppression (aplastic anemia and agranulocytosis), exfoliative dermatitis, and even Stevens–Johnson's syndrome. Valproic acid is also reported to produce pancreatitis. If not detected in time, these reactions may be fatal. Hence, periodic monitoring of hepatic and hematopoietic parameters is recommended, although there is no evidence that routine testing detects those serious conditions much prior to a time when the effects can still be prevented.

   Precise frequency of serious side effects from the traditional AEDs is unknown. Probably the incidence is somewhat higher than their spontaneous occurrence except in the case of **hepatotoxicity** associated with valproic acid. The highest risk group includes children below the age of 2 years receiving polytherapy, which includes valproic acid, the incidence being as high as 1 in 500.

   Usually benign leukopenia occurs in 10% to 20% patients, especially on carbamazepine. A total white cell count of 2,000 per cmm and an absolute granulocyte count of 1,000 per cmm are well-tolerated.

   Valproic acid is reported to produce thrombocytopenia, interference in the platelet aggregation, and an increased tendency toward bleeding. However, platelet counts above 60,000 per cmm are acceptable.
9. Because of its inhibition of cytochrome P-450 system, valproic acid in women is associated with abnormal metabolism of gonadal and adrenal sex hormones, often resulting in **PCOS.** It is characterized by infertility, hirsutism, obesity, increased serum androgen levels, frequent anovulatory cycles, and other menstrual abnormalities. The incidence of PCOS is 10% to 20% in women with epilepsy compared with 5% to 6% of women in the general population. The incidence of this syndrome is highest in women with PGE treated with valproic acid. How much each of the two factors, type of epilepsy and valproic acid, play a role in causing PCOS is still being debated.
10. **Teratogenic effects** occur in 5% to 10% pregnancies with the use of many traditional AEDs, highest incidence with valproic acid (see below).
11. Almost all of the traditional AEDs are associated with **bone loss,** even in young adults, and affect both genders following their use of 1 to 2 years. The bone loss is more severe in elderly patients, with polytherapy and with prolonged use. Possible mechanisms include hepatic induction of cytochrome P-450 enzymes (phenobarbital, primidone, phenytoin, and carbamazepine) leading to increased catabolism of vitamin D, secondary hyperparathyroidism, and increased bone turnover. Valproic acid, a noninducer, does produce bone loss by increased ostoclastic activity.

    Reduced bone density increases the risk, two to six times, for fractures, particularly of the hip and spine. Bone loss is best detected by dual-energy X-ray absorptometry and expressed as a T-score. Osteopenia is defined by a T-score of 21 to 22.5 and osteoporosis by a score 22.5.

Optimal management for bone loss is exercise, nutrition, and calcium and vitamin D supplementation. If osteoporosis is detected, treat with biphosphonate and other measures.

C. Pharmacokinetics. There are several undesirable pharmacokinetic issues related to the traditional AEDs.

1. Most of them are eliminated primarily through hepatic metabolism, through microsomal cytochrome P-450 enzymes; hence, there are several drug interactions. These enzyme-inducing AEDs lower hormonal levels including oral contraceptives, Warfarin, steroids, tricyclics, cyclosporine, digitalis, and antipsychotics. Carbamazepine is notorious in causing **autoinduction,** so that a smaller dose at the start is associated with blood levels which are achievable only by two to three times that dose after a month or so.

   On the other hand, competitive enzymatic inhibition increases the levels of these AEDs causing clinical toxicity. Erythromycin markedly inhibits metabolism of carbamazepine. Cimetidine and propxyphene have similar but lesser effects. These drugs, as well as grapefruit juice, may result in rise of carbamazepine to toxic levels.
2. Valproic acid is a strong competitive inhibitor of certain hepatic enzymes, increasing levels of many drugs including phenobarbital, lorazepam, lamotrigine, gonadal, and adrenal androgens.
3. Phenytoin and valproic acid have extensive **plasma protein binding** (80% to 95%), another undesirable pharmacokinetic property. Valproic acid, in addition, has nonlinear binding; at higher levels, the proportion of protein-bound drug is less, and there is a disproportionately high level of free or unbound drug. It is the free fraction that relates to drug efficacy and clinical toxicity.
4. Another troubling pharmacokinetic characteristic of phenytoin is its **nonlinear elimination** resulting from saturation of hepatic microsomal P-450 enzymes. Small increments (by 30 mg capsules) need to be made within the therapeutic window of 10 to 20 μg per ml. Giving a 100 mg capsule to a patient with a blood level of 15 μg per ml on a dose of 300 mg per day may lead to levels close to 30 μg per ml with the risk of clinical toxicity. Similarly, higher serum levels require a relatively small decrease in the dose to optimize the level.
5. **Shorter elimination half-lives** of some of the traditional AEDs (e.g., carbamazepine and valproic acid) necessitate giving them in three or four divided doses. However, the introduction of sustained- or extended-release preparations of these AEDs allows two divided doses ensuring better compliance.

VII. NEWER AEDS

Approximately 60% to 70% of patients with newly diagnosed epilepsy become seizure-free when treated with traditional AEDs as monotherapy. The remaining 30% to 40% are either unresponsive to traditional AEDs or obtain satisfactory seizure control only with polytherapy, but at a price of side effects and drug interactions. Furthermore, many of these AEDs are associated with neurotoxicity, teratogenic effects, drug–drug interaction, and many undesirable pharmacokinetic properties. Hence, newer AEDs are needed that may have a better side-effect profile, work through novel mechanisms to control epileptogenesis, and have more desirable pharmacokinetics. An **ideal AED** should be effective against multiple seizure types, effective against seizures resistant to traditional AEDs, have low neurologic and systemic toxicity, and should have favorable pharmacokinetics: complete oral absorption, minimal binding to plasma protein, primarily renal elimination, long elimination half-life, linear kinetics, and no enzyme induction or inhibition.

After a lapse of more than a decade, a number of new AEDs have been introduced in the United States, starting in 1993. Although none satisfy all the criteria of being an ideal AED, many show marked improvement when compared with the traditional AEDs. They are briefly discussed below. Their mechanism of action, indications, and side-effect profile are listed in Table 39.4, and the pharmacokinetics and dosages for adults are summarized in Table 39.5. Because a combined AED therapy is often used, knowledge of pharmacokinetic interactions between the AEDs is essential. These drug interactions are summarized in Table 39.6.

TABLE 39.4 Mechanism of Action, Indications and Undesirable Side Effects of Newer AEDs

Medication	Year Approved	Mechanism of Action	Indications		Undesirable Side Effects		
			Approved	Off-label	Weight	OCP	Other Significant
Felbamate	1993	↓ Na, ↑ GABA,	Intractable[a] partial epil. (adj, mono) ↑	–	↓	–	Aplastic anemia, hepatitis, insomnia, GI upset
		↓ Glutamate	SGE (adj, mono)				
Gabapentin	1993	↓ Ca ($\alpha_2\delta$ subunit binding)	Partial epil. (adj)	Partial epil. (mono)	↑	–	–
Lamotrigine	1994	↓ Na,	Partial epil. (adj)	(a) JME, (b) PGE with absences	–	–[b]	Skin rash, SJS
		↓Glutamate	Partial epil. (mono. conversion)	(c) Newly dx. epil. (mono)			
Topiramate	1996	↓ Na, ↑ GABA,	Partial epil. (adj)	(a) PGE with GTC & other seizure types	↓	±	Renal stone, paresthesia, glaucoma, metabolic acidosis, cognitive dysfunction
		↓ Glutamate	GTC (mono)	(b) SGE			
Tiagabine	1997	↑ GABA	Partial epil. (adj)	–	–	–	Absence status in PGE
Levetiracetam	1999	SV_2 binding decreases transmitter release	(1) Partial epil. (adj)	(a) JME (mono),	–	–	Anxiety, behavior disorder
			(2) Myoclonic seizure of JME (adj)	(b) PGE with other szs (c) SGE			
Oxcarbazepine	2000	↓ Na	Partial epil. (adj) & (mono)	–	–	+	Hyponatremia, skin rash
Zonisamide	2000	↓ Na, ↓ Ca (T), ↓ Glutamate	Partial epil. (adj)	PGE	↓	–	Renal stone, paresthesia
Pregabalin	2005	↓ Ca ($\alpha_2\delta$ subunit binding)	Partial epil. (adj)	–	↑	–	Euphoria
Lacosamide	2008	↓ Na, slow inactivation	Partial epil. (adj)	–	–	–	Prolonged P-R interval
Rufinamide	2008	↓ Na	Partial epil. (adj), Szs with Lennox–Gastaut syndrome	–	–	–	

[a]Used only for refractory epilepsy when possible benefits outweigh known serious liver and bone marrow toxicity.

[b]OCP decrease the level of lamotrigine.

JME, juvenile myoclonic epilepsy; SGE, secondary generalized epilepsy; Na, sodium currents; Ca, calcium currents; GABA, γ aminobutric acid transmission; OCP, oral contraceptive pill; SV_2, synaptic vesicle protein 2; SJS, Stevens Johnson syndrome; ↓, decrease; ↑, increase; –, no effect; ±, dose dependent effect; Ca (T), low threshold T current; adj, adjunctive; mono, monotherapy.

TABLE 39.5 Pharmacokinetics and Adult Dosages of Newer AEDs

AED	Bio-availability (%)	Peak Plasma Level (hr)	Volume of Distribution (L/kg)	Protein Binding (%)	Elimination Half-life (hr)	Time to Steady State (d)	Elimination Route	Starting Adult Dose (mg/d)	Escalation Dose (mg)	Usual Adult Maintenance Dose (mg/d)	Dosing Regimen (times/day)	Target serum level[a] (μg/ml)
Felbamate	>90	1–4	0.75	25	15–25[b] 11–15[c]	3–6	H 50 R 50	1,200	600/wk	1,200–3,600	2, 3	40–100
Gabapentin	30–60	1–4	0.8	0	5–9	1–2	R	300	300/2–7 d	900–3,600	3, 4	4–20
Lamotrigine	>90	1–4	0.9–1.4	55	24[b] 15[c] 60[d]	3–15	H 90 R 10	50[b,c] 12.5[d]	50/2 wk 12.5/2 wk	200–600[b,c] 100–200[d]	1, 2	2–20
Topiramate	>80	1–2	0.6–0.8	15	20–30[b] 12–15[c]	3–5	H 40 R 60	25–50	25–50/wk	200–600	2	2–20
Tiagabine	>90	1–2	1.0	96	6–9[b] 4–6[c]	1–2	H	4	4/wk	32–56	2–4	0.1–0.3
Levetiracetam	100	1–2	0.5–0.7	<10	6–8	2	R 66	1,000	500/wk	1,000–3,000	2	5–40
Zonisamide	>50	1–4	1.5	40	50–70[b] 25–40[c]	7–15	H 65 R 35	100	100/2 wk	200–600	1, 2	10–40
Oxcarbazepine[e]	>95	5–8	0.75	40	7–11	2	H	600	300/3–7 d	1,200–2,400	2	15–35
Pregabalin	>90	1–2	0.5	0	6–7	1–2	R	150	50–75/1–2 wk	300–600	2, 3	0.06–12.5
Lacosamide	100	1–4	0.6	<15	13	3	H 60 R 40	100	50/wk	400	2	–
Rufinamide	>85,↑ by food	4–6	0.8–1.2	<34	6–10	2	H	400–800	400–800/2 d	3,200	2	5–55

H, hepatic; R, renal; numbers are approximate percentage for each route.

[a]These are not therapeutic ranges, but levels commonly encountered in treated patients.

[b]When administered alone.

[c]When administered with enzyme-inducer AEDs (e.g., phenobarbital, phenytoin, carbamazepine and primidone).

[d]When administered with valproic acid.

[e]Kinetic parameters refer to monohydroxy derivative, for which oxcarbazepine is a prodrug.

TABLE 39.6 Pharmacokinetic Interactions among AEDs

Plasma Concentration Change to a prior AED Regimen

Added AED	CBZ	PHT	PB/PRM	VPA	CLZ	ESM	FBM	GBP	LTG	TPM	LTC	TGB	ZNS	PGL	OXC	LCM	RFM
CBZ	NA	?	↓	↓	↓	↓	↓	–	↓	↓	–	↓	↓	–	↓	–	↓
PHT	?	NA	?	↓	–	↓	↓	–	↓	↓	–	↓	↓	–	↓	–	↓
PB/PRM	?	?	NA	↓	↓	↓	↓	–	↓	↓	–	↓	↓	–	↓	–	↓
VPA	↑E	?	↑	NA	–	↓	↓	–	↑↑	↓	–	–	↓	–	–	–	↑
CLZ	–	–	–	–	NA	–	–	–	–	–	–	–	–	–	–	–	–
ESM	–	–	–	↓	–	NA	–	–	–	–	–	–	–	–	–	–	–
FBM	↑E	↑	↑	↑	–	–	NA	–	–	–	–	–	–	–	–	–	?
GBP	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–	–	–
LTG	–	–	–	–	↑	–	–	–	NA	–	–	–	–	–	–	–	–
TPM	–	↑	–	–	–	–	–	–	–	NA	–	–	–	–	–	–	–
LTC	–	–	–	↓	–	–	–	–	–	–	NA	–	–	–	–	–	–
TGB	–	–	–	↓	–	–	–	–	–		–	NA	–		–	–	–
ZNS	–	–	–	–	–	–	↑	–	–	–	–	–	NA	–	–	–	–
PGL	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–	–
OXC	↑E	↑	–	–	–	–	–	–	–	–	–	–	–	–	NA	–	–
LCM	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	NA	–
RFM	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	?	NA

↓, decrease; –, no change; ↑, increase; ↑E, CBZ-epoxide only elevated, CBZ may be decreased.

The utility of many newer AEDs is still evolving but there is a clear trend for increasing their use in partial and generalized epilepsy, refractory to traditional AEDs.

A. Efficacy.

1. Most of the newer AEDs are approved by the FDA for adjunctive therapy in the treatment of partial epilepsy refractory to traditional AEDs. The exception are felbamate and rufinamide, which are approved, also, for seizures associated with secondary generalized epilepsy of the Lennox–Gastaut's type.
2. Oxcarbazepine is now approved as monotherapy because of a better side-effects profile and more desirable pharmacokinetics; it is preferred over carbamazepine as the initial drug of choice for partial epilepsy.
3. Levetiracetam, lamotrigine, topiramate, and zonisamide have broad-spectrum activity against seizures associated with both focal and generalized epilepsies.
4. Lamotrigine has shown efficacy against absences and tonic–clonic seizures generalized from the onset. It is increasingly used to treat patients with PGE to avoid the side effects associated with valproic acid, especially in women.
5. Similarly, topiramate is approved for generalized tonic–clonic seizures (primary or secondarily generalized) and levetirecetam is found to be effective against myoclonic seizures associated with PGE.
6. Gabapentin and tiagabine are not used as often as others because of less efficacy and sedative side effects.

B. Side effects.

1. Many of the newer AEDs (e.g., oxcarbazepine, gabapentin, zonisamide, and tiagabine) are associated with neurotoxic side effects similar to those with traditional AEDs. Lamotrigine, levetiracetam, and topiramate have relatively less neurotoxicity in the commonly used daily doses.
2. Serious reactions are rare with newer AEDs with the exception of a high incidence of **felbamate-associated aplastic anemia and toxic hepatitis** detected after its release. This has led to a marked drop in its use.
3. Lamotrigine causes a **skin rash** in 5% to 10% of patients, and even **Stevens–Johnson's syndrome** may occur, although rarely. These complications are more common with rapid titration of the dose and comedication with valproic acid.
4. Topiramate produces **cognitive dysfunction,** for example, slower mentation, word-finding difficulty, problems in concentration, thinking abnormalities, impaired memory, and encephalopathy. These are less common with daily doses below 400 mg. Rarely, acute myopia associated with the secondary angle closure **glaucoma** has been reported.
5. Levetiracetam is associated with anxiety and **behavioral side effects.**
6. Zonisamide and topiramate may produce **renal calculi** in approximately 1% patients as well as **paresthesiae** in the limbs.
7. Like carbamazepine, oxcarbazepine is associated with **marked hyponatremia** in 3% of patients, more often in elderly patients or those who are on other medications. It becomes evident in the first few months of therapy but rarely necessitates discontinuation of the drug.
8. Lacosamide may prolong the P-R interval; hence, it should be used with caution in patients with known cardiac problems.

C. Newer AED versus traditional AEDs. Newer AEDs have substantial advantages over traditional AEDs including absence of side-effects, none or fewer drug interactions, and favorable pharmacokinetics. However, there is no evidence that any new AED has better efficacy compared with carbamezapine, phenytoin, or valproic acid in well-control trials of recent onset epilepsy.

D. Pharmacokinetics.

1. Except zonisamide and gabapentine (dose-related absorption), all the newer AEDs have 90% or more bioavailability with oral intake.
2. Hepatic metabolism is significant only with zonisamide and tiagabine, but they do not cause significant enzymatic induction.
3. Lamotrigine and oxcarbazepine, although metabolized in the liver, do not involve cytochrome P-450 enzyme system (phase I reaction). They undergo extensive metabolism by glucuronidation (phase II reaction).

4. Topiramate, levetirecetam, gabapentine, and pregabalin are eliminated either completely or largely by renal route without undergoing significant hepatic metabolism.
5. Oxcarbazepine and topiramate do induce the metabolism of oral contraceptives, but the effect of topiramate is significant only with doses over 400 mg per day.
6. Most of the newer AEDs, with the exception of tiagabine, has either no or clinically insignificant binding to the plasma proteins.
7. All of the newer AEDs have linear kinetics and no autoinduction.
8. Significant drug-to-drug interactions are absent with the use of gabapentine, pregabalin, levetiracetam, and zonisamide.
9. Most relevant interaction is between valproic acid and lamotrigine; valproic acid decreases the metabolic elimination of lamotrigine, increasing its half-life three to four times. In patients on valproic acid, lamotrigine needs to be started at a very low dose, titrated up very slowly, and the maintenance dose needs to be much smaller (100 to 200 mg) than when lamotrigine is used either alone or with enzyme-inducing AEDs, such as carbamazepine.
10. There has been little available data regarding the effect of newer AEDs on bone density or teratogenicity. Pregnancy registries have provided the most extensive data only on lamotrigine, which has a low adverse effect on fetal development.

VIII. STATUS EPILEPTICUS

A. Definition. The definition of status epilepticus has evolved over last two decades. The World Health Organization defines status epilepticus as follows: "A condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition." Most critical is the duration of seizure activity, and 30 minutes is the most commonly used duration. Hence, status epilepticus is considered to be present if continuous seizure activity persists for at least 30 minutes or two or more sequential seizures repeat within 30 minutes without full recovery of consciousness between seizures. Because the neuronal injury increases with duration, some experts now suggest that if seizure activity persists beyond 5 minutes, or, if at least two seizures have occurred over this period without full recovery, one may consider status epilepticus and treat it as such.

B. Types. Overall incidence is 1 in 5,000, and an estimated number of 60,000 new cases of status occur in the United States per year. Any type of seizure can manifest as status epilepticus, but the common forms include the following:

1. **Generalized convulsive status epilepticus (GCSE)** manifests as repeated major motor convulsions without full recovery of consciousness between seizures. In the past, the term *status epilepticus* implied essentially this form of status.
2. **Nonconvulsive status epilepticus** produces a continuous or fluctuating "epileptic twilight" state. This includes absence status and complex partial status. Only an EEG can establish the diagnosis.
3. **Simple partial status epilepticus** is characterized by repeated focal motor seizures, epilepsia partialis continua, and focal impairment of function (e.g., aphasia) without accompanying alteration of consciousness.

C. Cause of GCSE. GCSE is the most common and most serious type of status epilepticus. Unconsciousness associated with convulsive major motor seizures is the cardinal feature. The motor activity varies in symmetry and form depending on the history of seizures, duration of status, duration of treatment, and associated pathologic processes in the brain. GCSE occurs mainly in the following settings:

1. **Acute cerebral insult** or **acute encephalopathy** accounts for one half of cases of GCSE. These disorders include meningitis, encephalitis, head trauma, hypoxia, hypoglycemia, drug intoxication (e.g., cocaine), drug withdrawal, and strokes or metabolic encephalopathy.
2. GCSE can occur in patients with a **history of epilepsy** due to remote neurologic insults. Common precipitants of GCSE include changes in AEDs, sudden discontinuation or reduction in AEDs, systemic infection, physical and emotional stress, and sleep deprivation.

3. It can occur as an **initial unprovoked epileptic event** in an otherwise healthy person. Such "idiopathic" cases may account for one-third of all cases of GCSE.

D. Prognosis. GCSE is an emergency associated with substantial morbidity and mortality. The overall mortality may be as high as 30% among adults. GCSE associated with acute neurologic insults has the poorest prognosis, which essentially depends on the underlying cerebral etiologic factor.

When GCSE is the first epileptic event for an otherwise neurologically intact patient, or when it occurs in a patient with a previously known history of epilepsy but has a benign or reversible cause (e.g., hypoglycemia or drug or alcohol withdrawal), the prognosis is good if therapy is instituted promptly.

Without adequate and prompt treatment, GCSE can progress to a state of electromechanical dissociation in which the patient becomes increasingly unconscious or encephalopathic from the ongoing status, but the convulsive activity becomes increasingly subtle although EEG continues to show an ictal pattern. Patients with this condition, which is often called **subtle status epilepticus,** are considered to be candidates for an aggressive therapy, as are those with overt GCSE.

E. Management of GCSE. Immediate treatment needs to be instituted after establishing that the patient has an ongoing seizure lasting over 5 minutes, or has had two separate tonic–clonic seizures over a short period without recovery in between. The treatment protocol outlined in Table 39.7 is useful in the management of GCSE.

1. Diagnose status epilepticus by observing either continued seizure activity beyond 5 minutes or two generalized convulsions without full recovery of consciousness.
2. **Assess vital functions** and systemic abnormalities and stabilize the vital functions as much as possible.
   a. **Maintain an adequate airway and oxygenation.** This usually can be accomplished with an oral airway. The airway should be suctioned periodically to maintain patency. Oxygen should be administered through a nasal cannula or with a mask and a bag-valve-mask ventilator. If, after bagging, respiratory assistance is still needed, endotracheal intubation should be considered.

TABLE 39.7 Treatment Protocol for Status Epilepticus (Generalized Tonic–Clonic) in Adults

Time (min)	Treatment
0–5	Diagnose status by observing either continued seizure activity or one additional seizure
	Assess vital functions, insert oral airway, and give oxygen
6–10	Establish IV infusion line with normal saline solution. Monitor temperature and BP
	Draw blood for electrolytes, glucose, Ca, Mg, AED levels, CBC, BUN, and AST
	Administer 100 mg of thiamine followed by 50 ml of 50% glucose IV push
11–20	Give lorazepam 0.1 mg/kg IV push at a rate of <2 mg/min
21–60	Whether or not lorazepam stops the seizures, administer phenytoin 20 mg/kg IV no faster than 50 mg/min. Preferably, use fosphenytoin IV in PE doses
	Monitor BP and ECG during phenytoin (or fosphenytoin) infusion, and if hypotension or ECG changes occur, slow the infusion or temporarily withhold the drug. If seizures continue, give an additional 5–10 mg/kg of phenytoin (or fosphenytoin)
>60	If seizures continue, intubate the patient, transfer to ICU, and start continuous EEG
	Start pentobarbital (or propofol or midazolam) coma. Use an IV loading dose to produce at least a suppression-burst pattern on EEG. Continue a maintenance dose by IV drip to maintain seizure free state or at least suppression-burst pattern on EEG
	Slow the rate of infusion after 24–96 hr periodically to determine whether seizures have stopped clinically and on EEG
	Monitor continuous EEG, BP, ECG, and respiratory function

Abbreviations: Ca, calcium; Mg, magnesium; AST, aspartate aminotransferase.

b. **Assess blood pressure (BP)** and maintain it at a normal or high-normal level during prolonged GCSE. Use vasopressors if necessary.
c. **Establish an IV infusion line** using normal saline solution. Blood should be drawn initially for CBC, blood sugar, blood urea nitrogen (BUN), serum electrolytes (including calcium and magnesium), and AED levels, and both urine and blood should be obtained for toxicology screening.
d. **Assess oxygenation** by means of oximetry or periodic arterial blood gas determination.
e. **Monitor rectal temperature.** Body temperature can increase to a high level during prolonged status epilepticus as a result of increased motor activity.
f. If hypoglycemia is documented or if it is impossible to obtain prompt blood sugar determination, **administer 50 ml of 50% glucose** by means of IV push. In adults, **thiamine** (100 mg) is always given before glucose to protect a thiamine-deficient patient from exacerbation of Wernicke's encephalopathy.
g. Administer bicarbonate therapy only if serum pH is so low as to be immediately life-threatening. Acidosis commonly develops during GCSE, but acidosis usually responds promptly once the seizure activity is controlled.
h. For rare patients with GCSE resulting from hyponatremia (serum sodium concentration <120 mEq per L), hypocalcemia, or hypomagnesemia, administer appropriate electrolytes by means of IV drip.

3. **Drug therapy for the control of GCSE.** The goals of therapy are rapid termination of the clinical and EEG evidence of seizure activity and subsequent maintenance of a seizure-free state. Present recommendation is to treat GCSE by a combination of a short-acting benzodiazepine (such as lorazepam or diazepam) for rapid termination of seizure activity and a long-acting anticonvulsant (such as phenytoin or fosphenytoin) to subsequently maintain a seizure-free state. The use of IV lorazepam (2 mg) or diazepam (5 mg) by the emergency medical personnel prior to arrival in the emergency room is increasingly recommended for out of the hospital status.

In the emergency room, most physicians prefer IV lorazepam first, followed by fosphenytoin.

a. **Lorazepam** is administered at 0.1 mg per kg IV at a rate of <2 mg per minute. Diazepam has been largely replaced by lorazepam in the acute treatment of GCSE.

Although diazepam can stop GCSE slightly faster than can lorazepam, it has a much shorter duration of effectiveness allowing seizures to recur within 30 minutes of IV administration of diazepam bolus. Lorazepam has relatively rapid effectiveness and yet has a prolonged duration of action against status epilepticus. Both diazepam and lorazepam can produce serious respiratory depression or hypotension, particularly when given in combination with barbiturates.

b. **Phenytoin or fosphenytoin.** If seizures are still continuing after the administration of lorazepam, or even if they have been successfully terminated, IV administration of phenytoin (or preferably fosphenytoin) is usually needed to prevent recurrence of convulsions.
   (1) **Administration.** The usual loading dose of **phenytoin** is 20 mg per kg, given through a syringe into the IV port close to the patient at a rate <50 mg per minute. Injection is preferably performed by a physician. BP and ECG are continuously monitored throughout the infusion. The rate of infusion should be slowed or temporarily stopped if hypotension, widening of the QT interval, or arrhythmias develops.
   (2) There is a significant risk of **skin complications** when IV phenytoin is given. These include phlebitis, tissue sloughing after extravasation, and most serious, **purple glove syndrome** after infusion into a dorsal hand vein. The latter is a delayed soft tissue injury that can result in severe edema, arterial occlusion, and tissue necrosis that can necessitate amputation. These complications occur because parenteral phenytoin has 40% propylene glycol (antifreeze). Its pH is adjusted to 12.2 with sodium hydroxide (drain cleaner). Use of IV phenytoin is now virtually replaced by fosphenytoin, a much safer preparation for IV administration.
   (3) **Fosphenytoin,** a phosphate ester of phenytoin, is enzymatically converted to phenytoin by serum phosphatases. It is available only for parenteral use (IV or IM). Because it is dissolved in TRIS buffer at a pH of 8 to 9, fosphenytoin

does not cause tissue injury as phenytoin does. Three parts of phenytoin are bioequivalent to two parts of phenytoin, but the fosphenytoin dose is labeled in phenytoin equivalents (PE), so that 150 mg of fosphenytoin is labeled 100 mg PE. Although somewhat confusing, it apparently allows easy conversion of phenytoin to fosphenytoin dosing. Fosphenytoin can be administered more rapidly (up to 150 mg PE per minute compared with up to 50 mg per minute for phenytoin). The shorter infusion time compensates for the time needed for its conversion to active phenytoin. The result is that peak levels of phenytoin are attainable with IV fosphenytoin as rapidly as with phenytoin infusion itself. BP and ECG monitoring are recommended during fosphenytoin infusion, as they are with IV phenytoin.

(4) If the standard loading dose of 20 mg per kg of phenytoin (or 20 mg PE per kg of fosphenytoin) fails to stop GCSE, an additional 5 to 10 mg per kg may be given. Some patients may need high blood levels (30 to 40 μg per ml) before the seizure terminates. Phenytoin or fosphenytoin is effective in the treatment of 40% to 90% of patients with GCSE.

(5) Phenytoin or fosphenytoin should be used cautiously in the care of elderly patients, patients with known cardiac abnormalities, and patients with low baseline BP.

4. **Management of refractory GCSE.** If status fails to respond to combined lorazepam and fosphenytoin administration, the status is termed as refractory GCSE. There is a high probability that the patient has an acute cerebral insult responsible for the status and prognosis is more guarded, mortality being around 50%.

a. GCSE is successfully terminated in approximately 75% of patients by lorazepam, phenytoin (or fosphenytoin) combination. Remaining 25% constitute refractory GCSE.

b. The patient needs to be **intubated** now and placed in **ICU** for managing refractory GCSE.

c. The patient needs **general anesthesia** to eliminate not only clinical seizures but also electrical discharges indicative of continuing seizure activity. There is no randomized comparative study of the management of refractory GCSE on which to base the choice of the drug to induce general anesthesia. Continuous IV infusion of pentobarbital, propofol, and midazolam has been reported to be effective. The choice of a drug is largely based on the clinical experience of the physician. If one agent in optimal dosages is unsuccessful in controlling status, another should be tried. Continuous EEG monitoring is mandatory. The rate of administration of the drug is adjusted to ensure at least suppression burst or, as some experts recommend, cessation of all epileptiform activity, which may require making the EEG pattern almost isoelectric. However, the maximal EEG suppression is associated with an increased frequency of hypotension requiring the use of pressor agents. The anesthesia is continued for 1 to 4 days before an attempt is made to lighten it. If clinical seizures or ictal EEG patterns return, the infusion is appropriately increased.

Pentobarbital-induced anesthesia has been used for a long period for refractory GCSE. It is started intravenously with a loading dose of 5 to 15 mg per kg, followed by a maintenance dosage of 0.5 to 1.0 mg/kg/hour to maintain an EEG suppression-burst pattern or bring about cessation of all epileptiform discharges.

Propofol, a short-acting agent, is becoming the drug of choice. It is started IV with a loading dose of 1 to 2 mg/kg, given over 5 minutes, followed by a maintenance dosage of 1 to 5 mg/kg/hour to maintain suppression-burst pattern or complete control of all epileptiform discharges on the EEG.

Midazolam is administered at a loading dose of 0.2 mg/kg by slow IV bolus followed by a maintenance dose of 0.1 to 0.5 mg/kg/hour.

There are no prospective randomized trials comparing these three infusion agents for the treatment of refractory status. One systematic review demonstrated no difference between the three, at least for mortality rate. It appears that pentobarbital anesthesia, although, very effective, is associated with serious hypotension. Similarly, propofol if used in large doses (>5 mg/kg/hour) is associated with serious hypotension. On the contrary, midazolam appears to be safer and may be an excellent agent for refractory status epilepticus.

5. **Additional diagnostic studies.** When the seizures have been stopped or sufficiently controlled and the patient's vital signs have been stabilized, additional diagnostic studies, such as **chest radiographs, lumbar puncture, brain imaging,** and **EEG,** are performed to evaluate the cause of the GCSE and the effectiveness of the antiepileptic therapy.
6. **Long-term antiepileptic therapy.** After the episode of GCSE has been brought under control, most patients need continuation of some form of AED therapy. Long-term AED therapy is indicated when GCSE is caused by a structural brain lesion or when the patient has a history of epileptic seizures. When GCSE constitutes the patient's first seizure and no cause is found, the decision to initiate long-term AED therapy should be individualized, but most physicians initiate long-term treatment under such circumstances. If the GCSE was caused by acute CNS involvement, such as metabolic encephalopathy, meningoencephalitis, or cerebrovascular compromise, antiepileptic therapy is continued for a short period of 3 to 6 months.

F. Management of other types of status epilepticus. Other forms of status epilepticus do not pose the same emergency situation that GCSE poses. **Complex partial status epilepticus** has been reported to result in long-term neurologic deficits (e.g., permanent memory impairment) and should be controlled promptly with a benzodiazepine (e.g., lorazepam) followed by IV phenytoin (or fosphenytoin) or IV levitracetam. IV anesthesia is rarely indicated.

Management of absence status or simple partial status (focal motor seizure or epilepsia partialis continua without loss of consciousness) is not standardized. **Absence status** is best managed with an IV benzodiazepine (diazepam or lorazepam), which is effective in most cases. If a benzodiazepine is not effective, valproic acid can be given intravenously, in a dose of 25 mg per kg to promptly achieve therapeutic blood levels. After the absence status is controlled, valproic acid therapy is continued orally. **Simple partial status** responds to phenytoin (or fosphenytoin) usually in large doses to maintain blood levels as high as 30 g per ml. IV levitracetam or valproic acid are other alternatives. Benzodiazepines are not desirable because of their sedative side effects, except using one or two doses of IV lorazepam or diazepam initially.

IX. MANAGEMENT OF ACUTE SEIZURE CLUSTER

Some patients have repetitive series or clusters of epileptic seizures that occur within a short period, not meeting the definition criteria of status epilepticus. Such seizure clusters can be intermittently managed with either of the following approaches:

A. Most physicians use benzodiazepine (lorazepam or diazepam) to manage a cluster. **Lorazepam** is given in doses of 2 to 4 mg orally (sublingually) or parenterally (IM or IV), usually becoming effective in approximately 30 minutes. Administration may be repeated in doses of 1 to 2 mg with a maximum dose of 6 to 8 mg in 24 hours.

B. Diazepam gel (Diastat) is approved for rectal administration in the management of repetitive seizures. It is as effective, if not better, than lorazepam. Diazepam gel is administered in doses of 0.2 to 0.5 mg per kg rectally (usual adult dose is 10 to 20 mg); it is effective in 15 minutes and the effect lasts as long as 8 hours. If social or logistic reasons make the use of rectal administration difficult, sublingual or oral lorazepam is a better alternative.

C. Home treatment with rectal diazepam reduces the risk for subsequent status and the need for frequent visits to the emergency room in patients at risk for seizure-clusters or who have history of status epilepticus.

X. EPILEPSY, PREGNANCY, AND OTHER WOMEN'S ISSUES

A. Major problems. Pregnancy in a woman with epilepsy (WWE) is considered to constitute a high risk and needs to be followed by a high-risk obstetrician. Recently, American Academy of Neurology (AAN) has issued guidelines regarding the management of WWE, which are incorporated in the following discussion:

1. **Obstetrical complications.** In short, there is no conclusive evidence of increased obstetrical complications in WWE on AEDs.
   a. There is a weak evidence that WWE on AEDs has a slightly higher risk for cesarean section but a good evidence that this risk is not >2 times expected.
   b. There is a good evidence that there is no greater risk for late pregnancy bleeding, early contractions or early labor and delivery in WWE on AEDs. However, these complications are substantially increased in WWE who smoke.
   c. There is insufficient evidence to support or refute an increased risk for preeclamsia, hypertension, or miscarriage.
2. **Effect of pregnancy on epilepsy.** It is usually believed that seizures become more frequent during pregnancy in one-third WWE especially in second and third trimesters. According to the AAN guidelines, there is insufficient evidence to support or refute an increased risk in seizure frequency or occurrence of status epilepticus. Furthermore, if a WWE has been seizure free for at least 9 months prior to becoming pregnant, there is a high likelihood of her remaining seizure free during pregnancy.
3. **Alteration of the pharmacokinetics of AEDs** (increased clearance) results in decreased serum concentrations of almost all AEDs. Carbamazepine is least and lamotrigine is most affected. Changes in AED levels and in the hormonal status, poor compliance, psychological stresses, and sleep deprivation during pregnancy are some of the factors for exacerbation of seizures in some WWE.
4. The incidence of **fetal malformation** is two to three times higher among mothers with epilepsy than among women without epilepsy. Most of this effect is a result of fetal exposure to AEDs. Malformations include **minor malformations,** which are deviations from normal morphology not requiring treatment, and **major malformations,** requiring medical and/or surgical treatment. The overall incidence of major birth defects (oropalatal clefts, urogenital and congenital heart anomalies, and neural tube defects) among infants of epileptic mothers is approximately 7%, compared with 2% to 3% in women not receiving AEDs. All major AEDs have potential teratogenic effects, but certain facts have emerged from a number of pregnancy registries: Avoid the use of polytherapy during pregnancy and strongly consider monotherapy.
   a. Incidence of malformation increases with polytherapy compared with monotherapy. There is also an evidence for reduced cognitive outcome in the offspring of WWE receiving polytherapy during pregnancy.
   b. Valproic acid is associated with the highest incidence (6% to 10%) of major malformations, which include neural tube defects, facial clefts, and hypospadias. Hence, avoid the use of valproic acid in women during child bearing years.
   c. Valproic acid shows dose-related adverse effects on the fetus, the incidence of major malformation reaches three times with a dose above 1 g per day.
   d. Children born to women who received AEDs, particularly valproic acid, show higher incidence of developmental delay and lower mean verbal IQ, often requiring special education. This is yet another reason to avoid the use of valproic acid in women who want or may become pregnant.
   e. Phenytoin, carbamezapine, and phenobarb also, increase the risk of fetal malformation, cleft palate with phenytoin use, posterior cleft palate with carbamezapine use, and cardiac malformation with phenobarb use. Hence, avoiding the use of these AEDs during pregnancy would reduce major fetal malformations.
   f. Lamotrigine, which is the most extensively studied new AED, appears to have the least teratogenicity (3%), probably no different from the general population. However, there seems to be an increased risk for nonsyndromic orofacial clefts (cleft lip/palate). The UK registry has also shown dose-response effect of lamotrigine-associated malformations, 2% incidence with doses up to 200 mg per day compared with 5.4% for above 200 mg per day. Polytherapy use of lamotrigine with valproic acid markedly increases the incidence of malformation (12%).
5. **Adverse perinatal outcomes**: There is a good evidence that WWE taking AEDs have an increased risk of small-for-gestation offspring and a weak evidence for low apgar scores at 1 minute.
6. **Hemorrhagic disease** is reported among 7% of newborns delivered by women who have received hepatic enzyme-inducing AEDs (phenobarbital, primidone, phenytoin,

and carbamazepine) because of their effect in decreasing the vitamin K-dependent clotting factors. According to the AAN guidelines, there is insufficient evidence to support or refute an increased risk of hemorrhagic complications in the newborn of WWE taking AEDs.

B. Management guidelines. The therapeutic challenge is to keep the patient free of seizures while minimizing the adverse effects of seizures and AEDs on the course of pregnancy and the fetus. The major guidelines, which preferably are initiated before the patient becomes pregnant, are as follows:

1. Counsel the family about the higher incidence of fetal malformation, but assure the patient that most pregnant women (>90%) exposed to AEDs still bear healthy offspring.
2. May withdraw AEDs before pregnancy if the patient has remained free of seizures for >2 years. Do not wean AED if epilepsy syndrome (e.g., JME and MTS) suggests a high probability of recurrence.
3. Before conception, determine the best AED for seizure control. If the patient is on polytherapy, reduce AEDs to appropriate monotherapy. Because of the relatively high incidence of neural tube defects with valproic acid and carbamazepine, avoid these AEDs (both are schedule D drugs) and replace them with other AEDs. For women with PGE, lamotrigine alone or with levetirecetam or topiramate are alternative AEDs.
4. Prescribe folic acid in any woman during childbearing age, but certainly start it prior to the pregnancy (see below) to reduce the overall incidence of neural defects in the offspring.
5. Address and eliminate other risk factors, for example, drugs, alcohol, and smoking.
6. Do not stop or change AED therapy after the pregnancy has been diagnosed. The risk of fetal malformation is highest during the first 4 to 8 weeks of pregnancy. It usually is too late to protect the fetus by the time pregnancy is confirmed. Stopping or changing the drug can induce more frequent and more violent seizures with adverse consequences on both the mother and the fetus.
7. Supplemental multivitamins and folic acid are prescribed during the entire pregnancy. The precise dose for women with epilepsy has not been defined, but 1.0 mg per day is commonly used. Women at risk of having a child with neural tube defect (previous child or family history) are advised to supplement with 4.0 mg per day. Folic acid supplementation is recommended throughout childbearing age for sexually active women with epilepsy.
8. Monitor the AED serum level (preferably free level) before conception, at each trimester, in the last month of pregnancy, and through 8 weeks postpartum, especially if the patient is on lamotrigine, carbamezapine, or phenytoin. Adjust the dosage accordingly. Maintain lowest effective blood levels.
9. Measure serum **α-fetoprotein** and acetylcholinesterase levels at 15 to 18 weeks of gestation to be followed by high-definition **ultrasound imaging** to detect or neural tube defects and other major malfunctions. Together, these detect over 99% of the major fetal abnormalities. **Amniocentesis** is indicated only if these tests do not provide positive exclusion of a neural tube defect.
10. Give oral **vitamin K_1** (phytonadione) to the mother at 10 to 20 mg per day during the last month of pregnancy. Administer vitamin K_1 (1.0 mg IM) to the neonate immediately after birth. These measures help reduce the incidence of AED-related hemorrhagic disease of the newborn.
11. After delivery, check AED levels and adjust the doses of AED, usually at a lower level. Some AEDs, such as lamotrigine and oxcarbazepine, start reversing their elimination rate to the pre-pregnancy level even prior to the delivery. Their dose needs to be brought down within a week or so of the delivery.
12. **Breast-feeding** is allowed. Nearly all AEDs appear in breast milk at a concentration closely related to the AED's free plasma level. Hence, highly protein-bound AEDs attain only a very small concentration in the milk to produce significant clinical effect on the breast-fed baby. Even many of the newer AEDs, which are not protein-bound, deliver only a small daily dose to the baby. Most AEDs, with the possible exception of ethosuximide, phenobarbital, or primidone, do not reach sufficient concentrations in the breast milk to pose a serious concern for the infant. Problems such as poor suck, lethargy, irritability, or decreased weight gain have been reported in some infants nursed by women on these AEDs.

C. Prevention of pregnancy with oral contraceptives.

1. Women with epilepsy may use oral hormonal contraceptives if they wish. They do not exacerbate epilepsy despite the warnings on package inserts.
2. The major concern in using oral contraceptives is the higher failure rate (>6% per year) among women taking hepatic enzyme-inducing AEDs (e.g., phenytoin, carbamazepine, phenobarbital, primidone, felbamate, oxcarbazepine, rufinamide, and topiramate [doses over 200 mg per day]). This is due to increased elimination of both estrogens and progestogens by these AEDs. The effect is on many contraceptive preparations including combined contraceptive pill, combined patch, progestogen-only pill, and progestogen implants.

   The most commonly used is a **combined "mini-pill"** containing 35 μg or less of estrogen combined with progestogen. It may be less effective. Breakthrough bleeding can be a warning of decreased contraceptive efficiency. Patients taking these enzyme-inducing AEDs usually need a medium-dose combined contraceptive pill containing at least 50 μg of ethinyl estradiol. If breakthrough bleeding occurs, increase the dose to 75 or 100 μg per day. The **progestogen-only pill** is likely to be ineffective in women on enzyme-inducing AEDs. **Progestogen implants** are contraindicated. Intramuscular medroxyprogesterone injections (**Depo-Provera**) appear to be effective but patients are advised to take injections every 10 weeks rather than 12 weeks if they are on enzyme-inducing AEDs. Contraception using **Mirena coils** is highly effective and is not affected by enzyme-inducing AEDs because progestogen acts by being released locally in the uterus. It is a highly effective contraceptive option in women with poor compliance history.

   Because the usual 7-day pill-free interval decreases the contraceptive effectiveness, some recommend not only a higher dose estrogen-containing pill (e.g., 5 mcg estrogen) but using it in a **"tricycling regimen."** The pills are given consecutively for three cycles without a break, followed by a short pill-free period of 4 days. This tricycling method has the best contraceptive efficacy.

   Because both estrogens and progestogens are eliminated faster by enzyme-inducing AEDs, the higher dose of estrogen needs to accompany a similarly higher dose of progestogen in the combined contraceptive pill.
3. Non-enzyme inducers are unlikely to cause failure of oral contraception. These include valproic acid, lamotrigine, gabapentin, levetiracetam, zonisamide, pregabalin, and lacosamide.
4. Hormonal contraceptives have little effect on AEDs except on lamotrigine blood levels, which drop to half the precontraceptive levels because of enzyme induction. During the 7-day-off period, the levels could double back to pre-hormone levels. This effect may result in a breakthrough seizure during the 3 weeks of hormonal ingestion and toxicity during the off-week.

D. Catamenial epilepsy. Some women have increased frequency of seizures related to their menstrual cycle probably due to changing hormonal concentration during menstrual cycle. Catamenial seizures happen in about 10% of women and occur at three different times. Commonly, they occur either just before or during the first few days of menstruation (perimenstrual). Some have increased seizures at ovulation (midcycle), whereas others who have anovulation cycles have increased seizure activity in the second half of the menstrual cycle.

Perimenstrual increase may be treated by the intermittent use of **acetazolamide** at 250 to 500 mg per day starting 2 to 4 days before the anticipated onset and then continuing during menstruation.

An alternative is to cover the period of increased seizure frequency by additional doses of the AED or the use of a **benzodiazepine** such as lorazepam for a few days.

Hormone therapy is another alternative approach. Progestogen supplements may be given perimenstrually or during the latter half (10 to 26 days) of the menstrual cycle. A combined oral contraceptive pill or depot progestogen may also be used.

XI. AED TREATMENT OF THE ELDERLY

Prevalence of epilepsy increases sharply in the elderly. Common causes of seizures are cerebrovascular disease, degenerative dementia, and neoplasms in that order of frequency. Seizures

are nearly exclusively partial onset, being simple partial, complex partial, or secondarily generalized type. The postictal period is often longer in the elderly and may last several days after a generalized tonic–clonic seizure. EEG shows epileptiform abnormalities in 40% patients.

A. Major problems. Elderly patients with epilepsy constitute a special patient population because of age-related changes in the pharmacokinetics of AEDs, comorbidity, and multiple drug therapy. There is a decrease in plasma albumin with resultant overall decrease in protein binding of AEDs; hence, total concentration of highly bound AEDs (valproic acid, phenytoin, etc.) becomes misleading. Hepatic drug metabolism is decreased, and there is a steady decline in glomerular filtration rate, decreased tubular secretory function, and decreased renal blood flow with normal aging. These changes lead to longer elimination half-life and reduced clearance of many AEDs, with either primarily hepatic or renal elimination. In addition, concomitant medical problems and, consequently, multiple co-medications further affect the absorption, disposition, and metabolism of AEDs. Elderly patients also tend to experience more side effects of AEDs, especially somnolence, confusion, gait disturbances, and postural and other tremors.

B. Management guidelines for using AEDs to treat the elderly.

1. AEDs should be prescribed only when the diagnosis of epileptic seizures is firmly established and there is a high probability of recurrence.
2. AED therapy should be initiated at lower doses and titrated more slowly to a daily dose that is on average lower by 30% to 40% than used to treat younger adults.
3. For high protein-bound AEDs, measurement of free rather than total concentration may be more useful in evaluating seizure control or drug-related toxicity.
4. "Therapeutic ranges" of the traditional AEDs do not apply to the elderly mainly because of an overall decrease tolerability for drugs in this age group. Aim for a "low therapeutic" serum level, increasing the dose only if clinically necessary.
5. Carbamazepine, phenytoin, and valproic acid have been commonly used in the past because the seizures are focal-onset, but their pharmacokinetics makes them less ideal for the elderly. Oxcabazepine is well-tolerated and approved as monotherapy.
6. Generally, many of the newer AEDs are better for the elderly patient because of their fewer drug interactions, minimal or no protein binding, and predominant renal elimination (e.g., gabapentin, levetiracetam, pregabalin, or lacosamide). However, the dose has to be adjusted downward in the presence of renal impairment. Lamotrigine has only minor interactions and good tolerability; hence, it is another alternative among newer AEDs. These five newer AEDs are presently approved only for adjunctive therapy. Ongoing monotherapy trials may make them the initial AED of choice for seizures of the elderly. Many experts use off-label gabapentine or levetiracetam in the elderly.

XII. DISCONTINUATION OF AEDS

The decision to discontinue AEDs in the care of a patient who has been seizure-free for several years depends on many prognostic factors. The relapse rate after AED withdrawal is approximately 30% to 40% among adults with chronic epilepsy.

A. Prognostic factors.

1. **Types of epilepsy.**
   a. Some childhood forms of epilepsy (e.g., benign Rolandic epilepsy and childhood absence epilepsy) usually remit during adolescence.
   b. Patients with **PGE** with onset in adolescence or adulthood have a good prognosis. Many remit, but some (especially JME) need lifelong therapy.
   c. Patients with **focal epilepsy** (simple partial seizures, complex partial seizures, and secondarily generalized tonic–clonic seizures) have a high recurrence rate (40% to 50%) after discontinuing AEDs. This is especially true of adults with complex partial seizures, for which the relapse rate can approach or exceed 50%.
   d. Patients in whom seizures occur in the setting of an acute cerebral insult (e.g., trauma, infection, or stroke) may not have chronic epilepsy. Such patients should be considered for withdrawal of AED after a seizure-free period of 3 to 6 months.
2. **EEG findings** obtained just before discontinuation of AED therapy are useful predictors of the outcome. The relapse rate is four to five times higher if EEG shows persistent

epileptiform abnormalities. Hence, most physicians consider continuing AEDs if EEG continues to show paroxysmal abnormalities.

3. **Other predictors of outcome.** A high frequency of seizures, a long duration before seizures are controlled with AEDs, and multiple seizure types in a patient carry a less favorable prognosis. Similarly, patients who have structural abnormalities responsible for seizures or who have mental retardation or neurologic deficits are more likely to have recurrence of seizures after discontinuation of AEDs.
4. **Duration of seizure-free period.** There is no consensus on how long a patient should remain seizure-free before drug withdrawal is considered. Most physicians recommend a seizure-free period of 2 to 5 years, but such recommendations must be individualized because of the serious socioeconomic effect of recurrence of seizures.

B. General guide lines for withdrawing AEDs.

1. After assessing the risks and benefits, discontinuation of AEDs may be considered by the physician if the patient has been seizure-free for 2 to 5 years while taking AEDs, has had a single type of seizure, has normal neurologic examination, and normalized EEG with treatment.
2. Adult patients with PGE who have remained seizure-free for 2 to 5 years and whose EEGs show no paroxysmal abnormalities or photoparoxysmal response are good candidates for withdrawal of therapy unless they have JME.
3. Women who want to bear children and who have been seizure-free for several years should be considered for withdrawal of medication before conception to avoid possible ill-effects on the fetus.
4. On the other hand, most adults with focal epilepsy, secondary generalized epilepsy, or PGE manifesting as multiple seizure types probably need long-term, if not lifelong, AED therapy unless continuation of the medication and the seizure-free state are possible only at the cost of unpleasant side effects.

C. AED withdrawal mode and precautions.

1. AEDs must be withdrawn slowly, typically over 3 months or longer, especially in the case of barbiturates and benzodiazepines.
2. Patients taking more than one AED should have the less or least effective drug withdrawn before the first-line drug. Only after the patient has remained seizure-free, taking only one drug for several months, is the final drug withdrawn.
3. During the withdrawal period, the patient is advised to follow a restricted lifestyle (no driving or hazardous occupational or recreational activities) to minimize the consequences should the seizures recur.
4. If the seizures recur, the patient is promptly placed on an adequate dosage of an appropriate AED, which then probably has to be continued on a lifelong basis.
5. After the withdrawal period, attention has to be paid to such lifestyle issues as getting adequate sleep, avoiding alcohol, and avoiding anxiety that can cause recurrence.

XIII. REFERRALS

A. Psycosocial problems. Patients with epilepsy face many personal and psychosocial difficulties that require counseling. There is a high incidence of mood disorder; depression occurs in 20% to 50% patients. Driving restrictions, concerns regarding pregnancy, and possible transmission of epilepsy to the offspring are concerns that have to be addressed. It is important to detect these problems, respond to them promptly, and refer patients to appropriate specialists for further therapy and counseling. Patients should also be put in touch with local support groups, state epilepsy associations, and the Epilepsy Foundation of America. Patients who need comprehensive care can be referred to a local **comprehensive epilepsy center** equipped with multidisciplinary teams capable of providing psychosocial and vocational counseling in addition to the appropriate medical therapy.

B. Experimental AEDs. Approximately 20% to 30% of patients with epilepsy who have medically intractable seizures may be helped by referral to regional comprehensive epilepsy centers, which can conduct ongoing clinical trials of new AEDs. Such patients often need combination therapy with two or more AEDs, which is best handled in a comprehensive epilepsy center.

C. Surgical treatment.

1. **Resective surgery.** Patients who have medically refractory partial epilepsy with complex partial or secondarily generalized tonic–clonic seizures should be referred to a comprehensive epilepsy center for presurgical evaluation to determine whether they are suitable candidates for surgical treatment. Epilepsy is considered medically refractory when seizure control is unsatisfactory despite trials of three AEDs, in monotherapy or in combination. After multimodality presurgical evaluation, if found to have a single epileptogenic focus that does not involve eloquent cortex, these patients may be candidates for resective surgery.
   a. **Anterior temporal lobectomy** is the most frequently performed resective surgery when the seizures arise from antero-medial area or the lateral cortical area of the temporal lobe on one side. Epileptic patients with mesial temporal sclerosis on the MRI are excellent candidates because they are usually medically refractory but respond very well to surgery, two-thirds rendered seizure-free.
   b. **Extratemporal resection** for epileptogenic foci outside the temporal lobe is increasingly performed, although the success rate is 50% or less. Localizing an extratemporal seizure focus, for example, in the frontal lobe, is more challenging (may require invasive monitoring with subdural electrodes) unless a structural lesion is present on the MRI scan.
   c. **Corpus callosotomy** is performed in a few epilepsy centers for patients with secondarily generalized epilepsy who suffer from frequent drop attacks (atonic and/or tonic seizures). The procedure is followed by a number of complications such as disconnection syndrome, difficulty with motor and language function, and maintenance. Drop attacks and generalized seizures respond favorably but rarely do seizures totally remit.
   d. **Hemispherectomy** is reserved for a selected few patients who have unilateral hemispheric insult (Rasmussen's encephalitis, Sturge–Weber's syndrome, extensive cerebral dysgenesis, hemimegalencephaly, etc.), resulting in medically refractory focal epilepsy and hemiparesis.
   e. **Subpial transaction** is a surgical technique to treat focal epilepsy when the seizures arise from eloquent cortex such as the language or motor area. The procedure cuts horizontally connecting fibers so as to decrease propagation of seizure activity without resulting neurologic defects. The procedure is often combined with **corticectomy.**
2. **Vagal nerve stimulation.** The FDA has approved VNS as adjunctive therapy for medically refractory seizures in adults and children. VNS is considered for patients with focal or generalized epilepsy who have undergone unsuccessful polytherapy trials of several AEDs, including newer AEDs, who are not candidates for resective surgery or have undergone unsuccessful resective surgery.

   VNS requires implantation of a programmable signal generator subcutaneously in the upper chest on the left side. This device is capable of delivering intermittent stimulation to the left vagus nerve in the neck (by means of bipolar electrodes) at the desired settings. In addition, the patient or a companion can activate the generator by placing the accompanying magnet over the generator for several seconds to interrupt a seizure or reduce its severity if administered at seizure onset.

   The mechanism of action of VNS is unknown, but several large trials showed that approximately 30% to 40% of patients with refractory partial-onset seizures had a 50% or greater reduction in seizure frequency. Only a few had complete control of seizures. Overall, VNS has the same efficacy as many of the newer AEDs but without drug-related side effects. Patients with aurae are particularly helped because they can activate the device to abort an impending seizure. The common side effects include hoarseness, throat pain, coughing, dyspnea, and muscle pain. Possible surgical complications of hematoma, wound infection, left vocal cord paralysis, and injury to the vagus nerve or carotid sheath are rare when the procedure is performed by an experienced surgeon.
3. **Future trends.** Gamma knife surgery, deep brain stimulation of the anterior thalamic nuclei, and responsive neurostimulation (Neuropace) are some of the promising surgical techniques, which are being evaluated at present and may prove to be useful in providing better seizure control in the future.

Recommended Readings

Bourgeois BFD. Pharmacokinetic properties of current antiepileptic drugs. What improvements are needed? *Neurology*. 2000;55(suppl 3):S11–S16.

Browne TR. The pharmacokinetics of antiepileptic drugs. *Neurology*. 1998;51(suppl 4):2–7.

Browne TR, Holmes GL. *Handbook of Epilepsy*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.

Cloassen J, Hirsch LJ, Emerson RG, et al. Treatment of refractory status epilepticus with pentobarbital, propofol or midazolam: a systematic study. *Epilepsia*. 2002;43:146–153.

Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*. 1981;22:489–501.

Commission on Classification and Terminology of the International League against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389–399.

Engle J, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. Vol 2. Philadelphia, PA: Lippincott–Raven Publishers; 1997.

Engle J Jr, Wiebe S, French J, et al. Special report, practice parameter: temporal lobe and localized neocortical resection for epilepsy. *Epilepsia*. 2003;44:741–751.

French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy. *Neurology*. 2004;62:1252–1260.

French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy. *Neurology*. 2004;62:1261–1273.

Levy RH, Mattson RH, Meldrum BS, eds. *Antiepileptic Drugs*. 4th ed. New York, NY: Raven Press; 1995.

Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med*. 1998;338:970–976.

Mattson RH. Efficacy and adverse effects of established and new antiepileptic drugs. *Epilepsia*. 1995;36(suppl 2):S12–S26.

Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic–clonic seizures in adults. *N Engl J Med*. 1992;27:765–771.

Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic–clonic seizures. *N Engl J Med*. 1985;313:145–151.

O'Brien MD, Guillebaud J. Critical review, contraception for women with epilepsy. *Epilepsia*. 2006;47:1419–1422.

Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure free patients [summary statement]. *Neurology*. 1996;47:600–602.

Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. *Neurology*. 2009;73(2):126–132.

Report of the Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: management issues for women with epilepsy [summary statement]. *Neurology*. 1998;51:944–948.

Rowan AJ. Reflections on the treatment of seizures in the elderly population. *Neurology*. 1998;51(suppl 4):28–33.

Stowe ZN, Herzog AG, eds. *The Use of Antiepileptic Drugs, Long-Term Management Issues*. Stanford, CA: Stanford School of Medicine and Imprint Science; 2007.

Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: generic substitution for antiepileptic medication. *Neurology*. 1990;40:1641–1643.

Therapeutic and Technology Assessment Subcommittee of the American Academy of Neurology. Reassessment: vagus nerve stimulation for epilepsy. *Neurology*. 1999;53:666–669.

Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. *N Engl J Med*. 1998;339:792–798.

Wilder BJ. Management of epilepsy: consensus conference on current clinical practice. *Neurology*. 1998;51(suppl 4):1–43.

Working Group on Status Epilepticus. Treatment of status epilepticus. *JAMA*. 1993;270:854–859.

Zahn CA, Morrell MJ, Collins SD, et al. Management issues for women with epilepsy: a review of the literature. *Neurology*. 1998;51:949–956.

CHAPTER

40 Multiple Sclerosis

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Multiple sclerosis (MS) is a primary demyelinating disease of the CNS. The disorder appears to be immune mediated, although the actual development of the disease and the subsequent clinical course are probably influenced by genetic and environmental factors along with many factors that have not yet been determined. MS is an important neurologic disorder because of its prevalence, chronicity, induced disability, and tendency to affect young adults.

I. EPIDEMIOLOGY

The estimated number of patients with MS in the United States is between 350,000 and 450,000. MS is a disorder of young adults, with the onset of disease most frequently between the ages of 20 and 35 years among women, and 35 and 45 years among men. The prevalence of MS is approximately four times higher among women than among men, and the disease is much more common among white persons than among other races. Although there are no definite Mendelian patterns of inheritance with MS, first-degree relatives of the person with the index case have a 10- to 20-fold increased risk of the disorder. This genetic risk has been borne out in twin studies, in which the monozygotic concordance rate is approximately 30%, compared with 5% for dizygotic twins. HLA studies have shown a subtle but significant correlation between MS and different HLA antigens within various ethnic groups. Two different alleles have been liked to MS, but their actual influence is small. These are HLA-DRB1 and HLA-DQB1. The HLA-DRB1 has the larger effect of these genes, increasing the risk of developing MS 3-fold when present. Recent findings suggest a vitamin D response element to the promoter region of HLA-DRB1. It is suspected that vitamin D specifically interacts with HLA-DRB1 to alter its expression and thereby probably decrease ones susceptibility to develop MS. There are also non-MHC genes that induce a smaller effect. In summary, facts suggest that there is a genetic predisposition toward development of the disorder, but noninherited factors play a more dominant role.

II. PATHOGENESIS

The exact pathogenesis of MS remains elusive, but substantial clinical, laboratory data, and response to immune-modulating therapy suggest an autoimmune process. In immunologic terms, there is blood–brain barrier (BBB) breakdown allowing CD4 TH1 type lymphocytes into the CNS where they secrete inflammatory cytokines resulting in damage of myelin and amplification of the immune response. This damaged myelin is then stripped by a cell such as a macrophage and conduction anomalies develop. Less frequently the offending cell in a CD8 cytotoxic cell, directly damaging the oligodendroglia. Finally, there can be antibody-mediated destruction of the myelin, either directly or through activation of complement. B cell contribution will be discussed later in this section. Finally, oligodendrocytes death may occur, with or without apoptosis and support of development or repair of myelin ceases.

Myelin is important for saltatory conduction along the axon. Demyelination frequently occurs in localized areas. The result is a pathologic lesion called a **plaque.** These plaques are usually located deep in the cerebral white matter, near the ventricles, but they can occur anywhere, including gray matter, cerebellum, brainstem, spinal cord, and proximal nerve roots. This almost limitless variation of distribution is responsible for the variety of clinical presentations. The pathologic appearance of the plaque changes with repeated episodes of demyelination and chronicity. In an early active plaque, there is breakdown of the BBB with demyelination but typically relative sparing of the axons. Perivascular infiltrates of lymphocytes, macrophages, and occasionally plasma cells are present in small veins

and venules. Demyelination may spread outward from the plaque, especially along these vessels. Perivascular and interstitial edema may be prominent. At the edge of the plaque, there is hyperplasia of oligodendrocytes and activated astrocytes. These hyperplastic oligodendrocytes are probably involved in remyelination, but thin myelin sheaths found at electron microscopic examination suggest that this remyelination often is suboptimal and incomplete. In older plaques, oligodendroglia disappear, astrocytes show hypertrophy and hyperplasia (sclerosis), and axonal loss occurs. Evidence is present, by such techniques as MRI spectroscopy and histology studies, that there is substantial axonal dropout, in some patients, even in early disease.

The contribution of B cells, plasma cells, and antibody wax and wanes in popularity. The recent increase in the importance of B cells partially stems from the highly beneficial effects of rituximab on the disease course.

In MS patients, B cells sometimes appear in clusters or "germinal centers" in the CNS, and these areas appear to correlate with disease progression. At least a portion of these B cell may have been "immortalized" by Epstein–Barr viruses. B cells release inflammatory cytokines that up-regulate T cells and antigen-presenting cells and B cells sometimes become antigen-presenting cells. Antibodies can cause demyelination directly or through complement fixation.

The more recent advances in understanding the pathogenesis of MS involves T regulatory (T REG) cells and dendritic cells (DC). T REG cells are essential for the maintenance of immuno-tolerance, and their dysfunction is associated with the development of organ autoimmunity, as shown in both animals and humans. Data suggest that the dysfunction (temporary or permanent) of suppressor function of certain T REG cells is associated with MS. "Tolerogenic" DCs can modulate the expansion and function of T REG cells during CNS inflammation, or "immunogenic" DCs can induce effector T cell that result in demyelination. This interplay results in homeostasis or disease activity. MS seems to be associated with the dysfunction or impaired maturation of certain T REG-cell and DC populations. In the future, transient or even continuous augmentation of T REG-cell function could develop as an integral component of the therapeutic management of CNS autoimmunity and the course of MS.

III. CLINICAL FEATURES

Areas of CNS demyelination or plaques can produce **conduction abnormalities** with delayed or blocked conduction, impaired response to repetitive stimulation, or ephaptic conduction. The first three conduction defects can result in negative signs or symptoms. Depending on the extent of the conduction defect and location of the lesion in the CNS, the patient may have visual loss, numbness, weakness, ataxia, or nearly any loss of function attributable to a CNS lesion. Often the lesion comes and goes in a clinically silent area of the brain, the patient is not aware of any symptoms. Ephaptic conduction may result in positive signs and symptoms, including pain and paroxysmal syndromes. The variations of positive and negative signs and symptoms that may develop, further contribute to the complexity of the clinical disorder.

A. Presenting symptoms. Patients with MS may present with a variety of neurologic symptoms. The most common symptoms at onset are visual or oculomotor, accounting for 49% of the cases. Next are weakness or a sensory disturbance of one or more limbs, accounting for about 40% of cases. Twenty-three percent of patients come to medical attention with incoordination. Ten percent of patients have genitourinary or bowel dysfunction. Four percent have cerebral dysfunction. These percentages vary between reports.

B. Clinical course. Approximately 20% to 30% of patients with MS have a benign disorder. Some of these patients have only a few exacerbations; then the disorder appears to resolve. Others, typically with predominately sensory exacerbations, have recurrent events over years, without significant residual defects. More characteristically, all exacerbations do not fully resolve, and neurologic dysfunction accumulates gradually. Approximately 5% of patients have a highly malignant course with severe disability within months to a few years and, in some cases, even within weeks or days.

C. Disease forms. There are several forms of MS.

1. The most common form at presentation is **relapsing–remitting MS,** where neurologic dysfunction builds over days to weeks, reaches a plateau, and resolves over weeks to months. In some cases, the exacerbation is maximal within minutes to hours.
2. A very small group of patients have only partial or no recovery from the exacerbations, and disability accumulates in a stepwise manner. This disease is called **progressive-relapsing MS.**
3. More frequently, patients have relapsing–remitting disease that later becomes linear in progression. This disease form is classified as **secondary progressive MS** and accounts for most cases of MS later in the disease course.
4. The last subset accounts for a small number of cases of near linear progression from onset and is called **primary progressive MS.** The patients are typically older at disease onset, and the dysfunction manifest mainly as insidiously progressive spastic paraparesis with ataxia and bladder dysfunction. Even in the primary progressive form of MS, the condition of a substantial number of patients stabilizes after several years. Regrettably, there may be severe residual disability before stabilization. These patients need to be evaluated carefully for mimicking processes such as a mass, arteriovenous malformation (AVM), mechanical process, chronic infection, connective tissues disease, nutritional disorder, or an inherited spinal cord disorder or cerebellar disease.

D. Prognosis is difficult to access in patients with newly diagnosed MS. The most reliable prognostic factor is disease form. Patients with discrete exacerbations with significant recovery have the best prognosis. In this group, there is a trend toward better outcome when the onset of disease is at a younger age and the symptoms are restricted to one region of the CNS. This is especially true if the symptoms are predominantly sensory. Patients who begin with the primary progressive disorder usually have an insidiously progressive, but often, a more severe course. These patients usually have disease onset later in life and are more frequently men. Overall, the Kurtzke 5-year rule is reasonably reliable. This states that the absence of significant motor or cerebellar dysfunction at 5 years correlates with limited disability at 15 years.

IV. DIAGNOSIS

An accurate diagnosis of MS is extremely important because the disorder mimics many diseases of the CNS. Unfortunately, the diagnosis cannot be achieved reliably through any single paraclinical study. Rather, the entire clinical syndrome must be evaluated with a careful clinical history and examination. Those findings direct further laboratory studies to eliminate other disorders or to support the diagnosis of MS with paraclinical studies such as MRI, evoked potentials (see Chapter 33), and examination of the CSF (see Chapter 33).

A. Clinical aspects of diagnostic importance.

1. **Age.** The peak age at disease onset is between 20 and 45 years. It is rare for the disease to start before 14 years of age or after 60 years. Careful consideration must be given to other disorders in patients who have MS-like symptoms in an atypical age group.
2. **Character of signs and symptoms.**
   a. **Lesion localization.** Symptoms should suggest a CNS origin. Examples of exceptions include infranuclear cranial nerve palsy or monoradiculopathy due to plaque formation over the exit of the cranial nerve or nerve root within the CNS.
   b. **Onset features and course.** Most symptoms develop over hours to days, plateau, and then begin to decline. On occasion, the symptoms are maximal within seconds or minutes. Consideration should be given to infarction in these cases, especially if localization suggests a vascular territory. For all but patients with primary progressive MS, the most consistent history is relapses and remissions involving various areas of the CNS at different points in time. The diagnosis of primary progressive disease is more difficult. Presentation with aphasia, dementia, psychosis, acute anxiety, movement disorders, and intense pain is unusual in MS.
3. **Differential diagnosis.** Early on, a subset of patients with many CNS disorders have symptoms suggestive of the various disease forms of MS. A partial listing of conditions that may be similar to relapsing remitting MS with symptoms disseminated in space and time include adrenoleukodystrophy, lysosomal disorders, mitochondrial disorders,

CADASIL, systemic lupus erythematosus, Sjögren's syndrome, antiphospholipid antibody syndrome, sarcoidosis, CNS vasculitis, Behçet's disease, herpes zoster, Lyme's disease, progressive multifocal leukoencephalopathy (PML), syphilis, CNS lymphoma, vitamin B_{12} deficiency, and mass or spinal cord vascular malformations.

A partial list of disorders sometimes resulting in monoregional CNS involvement includes arachnoid cysts, cervical spondylosis, Chiari's malformation, syringomyelia, vitamin B_{12} deficiency, HTLV-I, leukodystrophies, AVMs, paraneoplastic syndromes, and CNS mass lesions. Because of the potential overlapping symptoms and findings, a clinician must always pursue a complete evaluation of patients with suspected MS and try to avoid forcing a diagnosis of MS in the setting of atypical features or findings, unless severe progression requires treatment. Then, if the patient does not respond appropriately to therapy reevaluation should be completed.

B. MRI. Overall, cranial MRI is the most sensitive paraclinical study in the diagnosis of MS. Lesions are most frequently detected with proton density-weighted images (first echo of a T2-weighted sequence) and the fluid attenuated inversion recovery (FLAIR) sequence (see Chapter 32).

1. **Frequency of MRI abnormalities in MS.**
   a. **Definite MS.** 85% to 97%.
   b. **Suspected MS.** 60% to 85%.
2. **MRI abnormalities.**
   a. Images typically reveal multiple focal periventricular areas of increased T2-weighted and FLAIR signals that are irregular in shape and <2.5-cm long. Unfortunately, none of these characteristics are specific to lesions secondary to MS.

      Abnormalities more suggestive of demyelination are multiple lesions, some of which are not punctate, but rather >6 mm in diameter. Often signal abnormalities are ovoid and abut perpendicular on the ventricular surface. These are a result of damage from T cell that have migrated out of small blood vessels that are perpendicular to the ventrical and penetrate the parenchyma. The T cells cause a cylinder of demyelination around these vessels with the resultant ovoid appearance on MRI. In MS, it is also common to find lesions involving the corpus callosum and pericallosal, juxtacortical, or infratentorial regions.
   b. Gadolinium-enhancing lesions are transient and reflect local temporary breakdown of the BBB with gadolinium leakage, as occurs in active plaque. The enhancement frequently disappears within 4 to 6 weeks. These contrast-enhanced MR areas reflect acute disease more accurately than do nonenhanced signal anomalies.
   c. T1-weighted sequence lesions ("black holes"), especially if they persist >6 months, correlate better with tissue destruction and subsequent disability.
   d. Atrophy is common in long-standing disease.
3. A compilation of these above features has been comprised to offer a more accurate radiological diagnosis of MS. The McDonald's criteria require at least three of any of the following: (a) ≥1 gadolinium-enhancing lesion OR 9 T2-hyperintense lesions if there are no gadolinium-enhancing lesions, (b) ≥1 infratentorial lesion, (c) ≥1 juxtacortical lesion, or (d) ≥3 periventricular lesions. One spinal cord lesion can substitute for one brain lesion.

C. Spinal fluid examination. The CSF examination is frequently performed in evaluation for MS, especially if the patient's clinical course or MRI is atypical for the diagnosis. Certain patterns of CSF abnormalities are highly suggestive of the disorder. These patterns are not specific to MS and can be seen with other inflammatory or infectious disorders (see Chapter 33).

1. The appearance of the CSF and the opening pressure are normal.
2. **Cell count.** The RBC count is normal. Mild lymphocytosis is typical; more than one-third of patients have >5 cells per mm^3. In the unusual event that >50 cells per mm^3 are found, consideration should be given to an infectious process.
3. **Protein.** The CSF protein level usually is mildly elevated. More than one-fourth of patients have a protein level >54 mg per dl. A protein of >100 mg per dl is rare.
4. **Myelin basic protein (MBP).** Myelin is destroyed in MS plaque. Approximately 30% of CNS myelin is **MBP.** MBP is released with the destruction of myelin, and its presence in the CSF is one of the most reliable indicators of current demyelination; the level

is proportional to the extent of myelin destruction. This elevated level is seen during the first 2 weeks after a substantial exacerbation in 50% to 90% of patients then disappears with time. MBP is not disease specific and can be seen in any process with myelin destruction, such as infarction or CNS infection.

5. **Immunoglobulin.** CSF immunoglobulin levels (primarily IgG, but also IgM and to a lesser extent IgA) are elevated (>12% of total protein) in 60% to 80% of patients with MS. The increase occurs because abundant plasma cells produce immunoglobulin in the brain and spinal cord. A smaller component of immunoglobulin arises from normal transfer from the serum and increased entry through a disturbed BBB.
   a. **IgG synthesis rate** is a calculated estimate of the rate of synthesis of IgG within the intrathecal space. It increases to >3 mg per day in 80% to 90% of patients with MS, but rarely >130 mg per day. This rate correlates with MRI plaque burden and decreases with corticotropin or glucocorticoid therapy. The rate increases in 12% of healthy persons and in 30% to 50% of patients with CNS infection.
   b. The **IgG index** is a calculation—(CSF IgG per serum IgG)/(CSF albumin per serum albumin)—that reflects the increased amount of IgG in the intrathecal space. The index is increased (>0.7) in 86% to 94% of patients with MS and often is the first CSF abnormality found in early disease.
6. **CSF oligoclonal bands (OCB)** are discrete bands frequently detected in the CSF of patients with MS. Most data indicate that OCBs are not directed against a specific antigen and are not involved in pathogenesis of disease. They are present in 30% to 40% of possible and 90% to 97% of definite cases of MS. OCBs are also present in other chronic inflammatory diseases of the CNS, infectious disorders, and 7% of healthy controls. Although the prevalence of OCBs increases when CSF is sampled later in the course of the disease, these bands are not related to current disease activity or therapy. A few bands are usually present. The presence of a single band usually means very little. The pattern of bands varies among different patients. In a single patient, the pattern tends to be relatively stable with some minor changes and addition of bands over a period of time. The bands in MS usually are seen only in the CSF when paired CSF and sera samples are evaluated simultaneously. This differs from the typically paired OCBs found in many other conditions such as inflammatory neuropathy, neoplasms, or systemic immune response.

D. **Evoked potentials** provide electrophysiologic evidence of conduction blocks or delays caused by demyelination. Before the availability of MRI, these studies were important to document widespread lesions. They still play an important role in the diagnosis of MS for some patients.

1. **Visual evoked potential (VEP).** Demyelination frequently occurs in the optic nerves and chiasm in patients with MS. Although some patients have symptoms consistent with optic neuritis, others have no associated visual symptoms. In most patients with previous demyelination of the optic nerve, VEPs typically remain abnormal for the duration of the patient's life. VEPs are abnormal in approximately 40%, 60%, and 85% of possible, probable, and definite cases of MS.
2. **Somatosensory evoked potentials** are obtained to detect conduction defects in the somatosensory pathways. They are abnormal in approximately 50%, 70%, and 80% of possible, probable, and definite patients with MS.
3. **Brainstem auditory evoked potentials** are obtained to evaluate conduction disturbances in the auditory pathways after auditory stimulation. They are abnormal in approximately 30%, 40%, and 70% of possible, probable, and definite cases of MS.

V. THERAPY

The complex, highly variable signs and symptoms of MS result in a clinical disorder that often is a challenge to manage. Therapy for MS is both symptomatic and immune modulating. Symptomatic therapy involves management of fatigue, spasticity, neurobehavioral disorders, paroxysmal disorders, pain, bladder dysfunction, and cerebellar dysfunction. Immune-modulating therapies are directed at altering the clinical course. This may involve management of acute exacerbations or the overall progression of the disease.

A. Symptomatic therapy. Patients with mild or early disease may have limited neurologic dysfunction and need minimal therapy. Among these patients, the main therapy is limited to counseling and education. Patients with more severe disease or later in the clinical course often have many symptoms that respond to treatment. Symptoms may vary, as conduction delays become conduction blocks, with subsequent loss of function, then revert with resolution of symptoms. This phenomenon may occur with fatigue where symptoms worsen later in the day or in the setting of infections or increased ambient temperature. A simple urinary tract infection (UTI) may cause a person who ambulates without difficulty to become bed ridden until after the UTI clears. These are not exacerbations but rather variations in ability to conduct action potentials.

1. **Spasticity** is common with severe or long-standing MS. Patients describe tightness or stiffness of the affected limbs or trunk and reflex spasms. These spasms can be provoked by a variety of stimuli or occur spontaneously. Spasticity can also increase after initiation of interferon-beta (INF-*ß*) therapy. Spasticity makes walking difficult, causes fatigue, makes transfer arduous, may interfere with sleep, and may cause pain. During an exacerbation or with otherwise asymptomatic UTI, there may be a significant increase in spasticity. Management of the underlying disorder often returns the spasticity to baseline. Range of motion exercises around each joint in the spastic limb may temporarily decrease spasticity and prevent fibrosis of the muscle. Pharmacologic agents usually are needed when a substantial amount of strength is wasted to overcome the spastic component to walk or when the patient is too weak to walk yet spasticity causes discomfort and difficulty with transfers. Overmedication should be avoided in the care of ambulatory patients because a small amount of extensor spasticity is beneficial for weight bearing in weak lower limbs.
   a. **Baclofen** is an effective agent for reducing spasticity, especially of spinal cord origin. The medication may be started at a low dose of either 10 mg at bedtime or 10 mg twice daily and slowly increased weekly or biweekly by 10 mg per day as tolerated or needed. When the dosage is too high, patients notice a decline in strength. At that point, decreasing the dose by 10 mg per day usually offers the optimal level of function with spasticity maximally treated but without significant induction of weakness. Higher doses often are tolerated and needed by patients with spastic paraplegia, for whom ambulation is not an issue. The maximal dosage recommended by the manufacturer is 80 mg per day in four divided doses; however, many physicians prescribe much higher doses. The most common side effects are the dose-related weakness, sedation, dizziness, and confusion. When the drug is discontinued, the dosage should be gently tapered because abrupt withdrawal can cause confusion and seizures. Baclofen can also be supplied via an intrathecal pump where very small doses of the medication can control severe spasticity. This is more effective than the oral route and has less systemic side effects.
   b. **Tizanidine** is effective in reducing spasticity by increasing presynaptic inhibition of motor neurons. Although related to clonidine, tizanidine has less potential for lowering blood pressure. However, care must be exercised when starting this medication because orthostatic hypotension can be induced. Consideration should be given to discontinuing or decreasing does of all antihypertensive agents before initiating the therapy because the combined effect with tizanidine can be profound. Tizanidine is started at 2 mg at bedtime and gradually increased to as high as 36 mg a day in three divided doses as needed or tolerated. The major side effects are somnolence, dry mouth, and asthenia. Tizanidine should be used with care to treat the elderly, who clear the drug slowly, and to treat patients with renal impairment. Oral contraceptives decrease the clearance of tizanidine by 50%. Finally, the medication is primarily metabolized in the liver and induces liver toxicity in some patients. It should be used carefully or not at all in the treatment of patients with impaired hepatic function or in patients taking other hepatotoxic medications. Liver function should be monitored before initiation of therapy and especially for the first several months of administration. Tizanidine and baclofen work together in a synergistic manner. Baclofen typically is administered first because there are fewer complications. If the patient does not respond adequately to the baclofen, tizanidine is slowly added. Often, both tizanidine and baclofen can be given at lower doses, yet with increased control of spasticity.

c. **Benzodiazepines** provide benefit to a subset of patients with severe spasticity refractory to baclofen and tizanidine. The addition of small doses of diazepam to baclofen or tizanidine can result in a synergistic effect. Usual doses are 0.5 to 1 mg two to three times a day. If patients are intolerant of baclofen, diazepam may be used alone. The dosage may be started at 1 to 2 mg two to three times daily, gradual increasing to a maximum of 20 to 30 mg per day. Dependence can develop, so the drug should be used with care and tapered slowly when discontinued.

d. **Dantrolene** may be used for spasticity when baclofen, tizanidine, and benzodiazepines are ineffective. Weakness induced by the drug limits its usefulness in many patients already compromised with motor impairment. In the rare patient whose strength is preserved in the presence of severe spasticity, the drug may provide benefit. Other patients who are good candidates for this therapy have severe weakness with no useful function of the legs and spasticity that contributes to flexion contracture, discomfort, and difficulty with transfer and activities of daily living. In this situation, the loss of strength is of less consequence. The dosage is usually started at 25 mg per day and gently increased to 100 mg four times a day if needed. Liver function must be monitored because liver toxicity is a rare but potentially fatal complication of this medication. The risk is highest among women, patients older than 35 years, and those taking a dosage >200 mg per day. Other side effects include diarrhea at higher doses and occasionally pericarditis or pleuritis. Although the drug usually has little effect on cardiac or smooth muscle, it should be used with care to treat patients with myocardial disease.

e. **Botulinum toxin type A** may be used for isolated spastic muscle groups. The toxin must be readministered every 2 to 4 months and antibodies against it may develop.

f. When these pharmacologic agents are contraindicated because of complications or do not control spasticity, **surgical intervention** may be considered. The procedures include percutaneous radiofrequency foraminal rhizotomy, sciatic neurectomy, intramuscular (IM) neurolysis, tenotomy, neurectomy, and myelotomy. Intrathecal baclofen delivered with a subcutaneous pump is an effective alternative for some patients. Again, this therapy should be reserved for patients with severe spasticity unresponsive to oral therapy or patients in whom oral agents caused severe complications. The pump is expensive, requires frequent dosage adjustments, especially during the first several months, and requires refilling every 1 to 3 months. The battery has a limited life and requires replacement along with the pump (not the catheter) every several years.

2. **Fatigue and heat sensitivity.** Most patients with MS report fatigue that varies from mild to severely disabling. This symptom can be potentiated by spasticity, depression, current infection, sleep disorders, or interruption of sleep due to nocturia from bladder dysfunction. After these causes are controlled, patients should be instructed to conserve energy through time management, economy of effort, and work simplification. A subset of patients report extreme fatigue and even exacerbation of focal neurologic symptoms in hot environments and increased body temperature during exertion or with a febrile illness. Heat-sensitive patients should be advised to decrease ambient temperature to comfortable levels, dress lightly to enhance heat dispersion, and aggressively control fevers.

a. **Amantadine** provides a modest reduction in fatigue for most patients. The dosage is 100 mg in the morning and early afternoon. The medication is discontinued if there is no benefit after 1 month.

b. **Modafinil** is effective in decreasing fatigue in many patients with MS without affecting memory, concentration, or learning. Before using the medication, patients must be informed that it is being prescribed in a nonapproved manner, and insurance companies may not provide coverage. Patients typically respond to 200 mg in the morning and often with an additional 200 mg given in the early afternoon. Doses >400 mg total each day are associated with increased side effects. The abuse potential for the drug is low, and no withdrawal symptoms appear when it is discontinued. Oral clearance of modafinil is reduced in the elderly, especially in patients with hepatic impairment, in which the serum concentration of modafinil can double. The most commonly observed adverse events in clinical trials included headache, nausea and vomiting, nervousness, anxiety, and insomnia. Modafinil can cause failure of oral contraceptives or hormonal

contraceptive-containing implants or devices owing to induction of the CYP3A4 isoenzyme metabolism of ethinyl estradiol or the progestins in these products.

c. **Pemoline** may be used for patients undertaking a short-term project or activity in which fatigue causes considerable dysfunction. The stimulant effect and abuse potential of this medication preclude long-term use. The initial dose of 18.75 mg every morning and may be increased to 37.5 mg or higher.

d. **Selective serotonin reuptake inhibitors (SSRIs)** often give an energy boost, even when the patient says there are no depressive symptoms. These drugs are typically quite safe. A trial may be merited in the care of a patient with severe fatigue.

3. **Neurobehavioral disorders.** Patients may have several neurobehavioral disorders, including depression, euphoria, emotional lability, dementia, or cognitive impairment, and in rare instances, bipolar disease, extreme anxiety, and psychosis. Recognition of these disorders is important because some are amenable to therapy, thereby decreasing disability and improving quality of life.

   a. **Depression** is common in MS. The reported prevalence varies considerably with a reasonable range probably between 25% and 60%. The cause of the depression is most likely multifactorial. When the depression appears to be a reaction to the illness, the patient may benefit from counseling and management of the MS. Although actual investigation of drug efficacy in MS is limited, for many patients, a trial of antidepressants should be considered.

      (1) **SSRIs** are the medication of choice for depressive symptoms in patients with MS. Other antidepressant agents have been used as well including serotonin-norepinephrine reuptake inhibitors and monoamine oxidase (MAO) inhibitors.

      (2) **Tricyclic antidepressants** may be used as a second-line choice when the anticholinergic side effects are of less detriment than is control of pain or when they actually control the type of bladder dysfunction that the patient exhibits.

      (3) **MAO inhibitors** may be used as a first line, a second line, or an adjunctive therapy for nonresponders of SSRIs.

      (4) **Electroconvulsive therapy** may have a limited role in the care of patients with MS. It has been complicated by exacerbations in anecdotal cases.

   b. **Other neurobehavioral disorders** include euphoria, pathologic laughing and crying, anxiety, and psychosis.

      (1) **Euphoria** is defined as a persistent change in mood consisting of cheerfulness and optimism. This mood may persist in spite of the patient's awareness of very suboptimal circumstances, including severe disability. Unfortunately, it is often associated with more advanced disease and brain atrophy. No treatment for the euphoria is required.

      (2) **Emotional lability** is common among patients with MS. This ranges from mild giggling or tearing to pathologic laughing and crying or, in severe cases, complete emotional incontinence. Usually the patient is aware of the lability, and these emotional outbursts are socially distressing. Amitriptyline improves emotional control for many patients. The drug may be given at bedtime, starting at 25 mg and increased as needed. Most patients respond to <100 mg. If amitriptyline is ineffective, a trial of levodopa or bromocriptine is merited.

      (3) Extreme **anxiety** is rare in MS. Alprazolam given at a dosage of 0.25 to 0.50 mg two to three times a day may decrease the symptoms. An alternative medication is diazepam. Both medications have abuse potential and should be prescribed with care and tapered gently when discontinued.

      (4) Although rare, **psychosis** does occur among patients with MS. This is typically associated with agitated depression or a complication of steroid therapy rather than an isolated phenomenon. Antipsychotic drugs are used as they are in the care of persons with psychiatric illnesses.

4. **Paroxysmal disorders** are typically intense ephaptic events that last seconds to minutes with a tendency to reoccur in a stereotypic manner. These occur in 1% to 4% of patients with MS without associated epileptiform activity on an EEG. Some are unique to MS and on occasion are the initial symptom. They may occur during an exacerbation or in isolation and frequently last weeks to months then spontaneously resolve. A careful

inquiry for the presence of these disorders is important because they can cause the patient considerable discomfort or dysfunction.

a. **Management of paroxysmal disorders.** Most paroxysmal disorders respond to anticonvulsant agents. The drugs of choice are levetiracetam, carbamazepine, or oxcarbazepine.
   (1) **Levetiracetam** is very effective in many patients and requires no laboratory monitoring. Furthermore, the medication does not induce the P-450 enzyme system of the liver and has very few drug interactions. Patients frequently respond to doses such as 250 or 500 mg twice a day. Often they respond but the dose has to be increased slightly after a few weeks due to induced drug tolerance. Usually the patient responds before the higher doses such as 2,500 mg twice a day are required.
   (2) **Carbamazepine** often provides relief, even at low doses such as 200 mg each day or twice a day. However, the medication may contribute to trunkal ataxia.
   (3) **Oxcarbazepine** is less likely than carbamazepine in inducing CNS side effects, such as truncal ataxia, or hematologic abnormalities, such as leukopenia. Drug levels are rarely monitored. However, hyponatremia may occur and the physician must consider periodic checks of sodium, especially during the first 3 months. The dosage of oxcarbazepine should be started at 300 mg PO each day and increased as indicated by 300 mg per day every third day or 600 mg per day at weekly intervals up to 2,400 mg per day in two divided doses.
   (4) If these therapies are ineffective, consideration may be given to phenytoin, acetazolamide, or phenobarbital.
   (5) Therapy should be tapered and discontinued after 2 to 3 months because the disorder may have resolved.
   (6) Additional information is included under trigeminal neuralgia because that disorder often is more difficult to manage.

b. **Trigeminal neuralgia** is characterized by triggered and nontriggered paroxysmal episodes of facial pain in the trigeminal distribution. It occurs in 1% to 2% of patients with MS. In MS, the pain is similar to that in the general population except that it occurs at a higher incidence, at a younger age, and is more often bilateral. Also, there is an increased incidence of atypical trigeminal neuralgia with longer episodes of intense pain superimposed on persistent facial discomfort. Levetiracetam, carbamazepine, or oxcarbazepine gives complete relief in some patients and reduces the pain in most. When trigeminal neuralgia is refractory to these medications, the orally active antipsychotic agent pimozide may be considered. This medication should be used with care because most patients with MS have adverse effects, including lethargy, impaired concentration, hand tremors, involuntary movements during sleep, and slight parkinsonian features. Other medications that may offer relief are clonazepam, amitriptyline, or misoprostol. When there are serious drug complications or a lack of pain control with conservative management, surgical intervention such as percutaneous stereotactic thermal rhizotomy or glycerol rhizotomy often is effective. The patient may need two to three treatments before complete control is obtained.

c. **Other paroxysmal sensory or painful symptoms** include a variety of sensations, including burning paresthesia, severe or aching pain, unpleasant quivering sensations, spontaneous Lhermitte's-like phenomena, and itching. Most of these episodes last seconds to a few minutes and most frequently involve the extremities, although they can affect any part of the body. Paroxysmal itching varies from the other sensations. The episodes last as long as 30 minutes, sometimes occurring in a dermatomal distribution, especially over the shoulders and neck.

d. **Tonic spasms** are severe spasms that last seconds to minutes. They begin in the limbs or trunk and spread upward or downward, sometimes crossing the midline. Many times, an intense pain or unpleasant sensation starts at a trigger zone and precedes or accompanies the spasm. In other patients, the spasms occur without discomfort. These spasms can be provoked by movement, tactile stimulation of a trigger zone, or hyperventilation, or they can occur spontaneously. In an individual patient, the tonic spasm, with or without the pain, reoccurs in a stereotypic pattern. These episodes can occur as part of an exacerbation or when the patient's condition is stable. Tonic

spasms should be differentiated from flexor spasms. With tonic spasms, the spasms are more intense, usually are associated with severe pain, spread in a stereotypic manner, and are not correlated with the degree of underlying spasticity. Although flexor spasms are best managed with baclofen, tonic seizures usually respond to the anticonvulsants previously mentioned.

e. **Paroxysmal dysarthria and ataxia.** These episodes usually last <1 minute but can reoccur several times in 1 day. In some patients, anxiety or hyperventilation precipitates the episodes. Ataxia can result in falls, and dysarthria can be so severe that speech cannot be interpreted. Although dysarthria and ataxia are always present, other symptoms can be associated, including diplopia, numbness, and weakness.

f. **Diplopia** can occur with dysarthria and ataxia or occur in isolation. Isolated episodes of diplopia last seconds to a few minutes and can occur as often as 100 times a day.

g. **Other paroxysmal disorders** include akinesia in one or more limbs that lasts a few seconds and frequently reoccurring several times a day, weakness usually of a leg or hand lasting 10 to 20 seconds to a few minutes with resultant unexpected falls or dropping of objects, and paroxysmal hemiataxia and crossed paraesthesia.

5. **Pain.** Although pain rarely is an initial symptom of MS, it commonly develops during the course of the disease and affects >50% of the patient population. The paroxysmal pain syndromes that respond best to anticonvulsant medications have already been discussed. More commonly, patients have chronic pain that includes dysesthetic pain, back pain, and painful leg spasms. The typical burning or aching dysesthetic pain responds best to the anticonvulsant gabapentin. Therapy usually is started at 100 to 300 mg at bedtime and increased as needed or tolerated to 2,400 mg per day in three divided doses or two smaller doses at morning and noon and a larger dose at bedtime. Patients frequently respond by the time they have taken 1,800 mg in divided doses in a day. The typical main side effect is fatigue. If gabapentin is ineffective or if side effects preclude its use, pregablin, 100 mg three times a day or 150 mg twice a day or antidepressant drugs such as venlafaxine HCL, duloxetine HCL, amitriptyline or imipramine may be used. Other medications that may offer benefit are capsaicin cream applied to the skin or topiramate, which has provided benefit to a subset of patients. A combination of aggressive physical therapy and nonsteroidal anti-inflammatory agents provides partial relief to most patients with chronic back pain. Addition of gabapentin or antidepressant medications may be necessary. Patients resistant to therapy and debilitated with severe pain may need intrathecal morphine, intrathecal phenol, or a neurolytic procedure such as dorsal rhizotomy.

6. **Bladder dysfunction.** Patients with MS frequently have neurogenic bladder at some point during the illness. In many, bladder dysfunction persists and causes major social concerns. This dysfunction may be caused by an uninhibited small capacity or a flaccid neurogenic bladder, a combination of these dysfunctions or detrusor–sphincter dyssynergia. The symptoms of uninhibited neurogenic bladder are primarily irritative, whereas those of a flaccid neurogenic bladder are primarily obstructive. There is a substantial amount of overlap between the symptoms, and a clinical history frequently is insufficient for diagnosis. Because several conditions are associated with MS, the optimal approach is for the patient to undergo a urologic evaluation to determine the exact bladder dysfunction. This is especially true because the therapies for these disorders are frequently directly antagonistic.

   Mechanical dysfunction often leads to UTIs. These can result in pseudoexacerbation with increased lower extremity sensory loss and weakness of tone that resolve when the infection is appropriately managed. One should avoid prescribing empiric antibiotics because resistant strains of bacteria often develop. Allow the therapy to be directed by the culture and sensitivity results.

7. **Sexual dysfunction.** Erectile dysfunction is common among men with MS. It can be caused by demyelination in the spinal cord from lesions of the motor and sensory pathways or decreased testosterone levels that can complicate the disorder. A variety of other issues, such as medications, fatigue, spasticity, paraparesis, and psychological issues, such as poor self-esteem and self-image, fear of rejection, fear of incontinence, or depression, can lead to erectile dysfunction. The cause of dysfunction should be sought vigorously. If the dysfunction appears to have a nonhormonal physiologic cause,

medications like sildenafil may be tried. Typically give 25 to 100 mg 1 hour before sexual intercourse. Other agents such as vardenafil or tadalafil may also be tried. Older traditional approaches may include intracavernous papaverine, prostaglandin E, phentolamine, vacuum devices, and a penile prosthesis.

Sexual dysfunction in women has not been as well studied as it has in men but may also be caused by several of the previously mentioned causes with the exception of decreased testosterone levels and the addition of pelvic floor weakness. When nonphysiologic issues have been excluded, sildenafil may effective in a small subset of women.

8. **Cerebellar dysfunction.** Cerebellar dysfunction is common, especially in the primary progressive form of the disease. Upper extremity ataxia and tremors may be so severe that activities of daily living are impossible, and nursing home care is required. This dysfunction is especially resistant to therapy. A trial of levetiracetam is merited and is very effective in some patients. The drug requires no laboratory monitoring. Furthermore, the medication does not induce the P-450 enzyme system of the liver and has very few drug interactions. Patients frequently are started at doses such as 250 or 500 mg twice a day and gradually increased to 2,500 mg twice a day. Patients often respond to lower doses, but the dosage frequently has to be increased after a few weeks due to induced drug tolerance.

   Despite reported benefit in small trials, isoniazid, carbamazepine, primidone, and glutethimide all provide only marginal control in most patients. Other medications that have been used with little success are baclofen, clonazepam, propranolol, choline, and lecithin. Surgical intervention is controversial and has included stereotaxic thalamotomy and deep brain stimulation. Exacerbations have occurred after surgery, and it is difficult to predict the response of tremors to surgical procedures. When a patient begins to have significant cerebellar dysfunction, consideration should be given to more aggressive immune-modulating therapy.

9. **Restoring conduction in areas of demyelination.** Dalfampridine (ampyria) is a broad-spectrum potassium channel blocker that increases conduction of action potentials in areas of demyelination in animal models. The drug was studied in MS patients by determining the speed of a 25-foot walk, with or without the drug. This "walking drug" was approved for MS in January of 2010. In actually, it may restore conduction in any area of demyelination and thus improve the majority of symptoms MS patients possess. The best response in our clinic was a patient who had not moved either leg in 20 years, and with dalfampridine, he is walking. This is not the typical response, and many of our patients show no improvement at all. When improvement is seen, it typically occurs within 3 weeks. The drug precipitates seizures in a small subset of patients and should not be used in a patient with a seizure disorder. It is cleared by the kidney, thus precluding it use in patients with significant renal dysfunction or renal failure. The medication is taken at 12-hour intervals. When the dosing interval is shorted too much, the level of the drug increases as do the side effects. Several potential side effects are listed in the package insert, but these usually appeared in the controls as well and are a result of the MS. A few of our patient feel the drug contributes to UTIs. If the drug is taken too late in the day, it may cause insomnia. The medication may contribute to ataxia, but in part, this may be expected in a deconditioned patient who again begins to ambulate. Finally, some of our patients feel the drug intensifies pain. This may be due to increased aberrant conduction.

B. **Immune modulating therapy.** Although the exact pathogenesis of MS is unknown, it appears to be multifactorial with a substantial autoimmune contribution. This has prompted numerous clinical trials of immune-modulating agents in an attempt to alter the course of the disease. Available therapies remain inadequate and have the potential for substantial complications. Vitamin D should be checked and/or administered to all patients, their siblings, and children. It appears that the vitamin induces T REG cells, which down regulate the immune response and turn off the gene which, when present, places individuals at the highest genetic risk.

1. **Management of exacerbations.**
   a. **Indications for therapy.** Exacerbations are common among patients with active relapsing–remitting or relapsing–progressive MS. There are few data to support changes in long-term clinical course or disability with management of exacerbations.

The advantage of therapy is to expedite recovery from an exacerbation to allow a person to return to a higher level of function more quickly than if the exacerbation had been allowed to run its natural course. We often find that many patients initially have an excellent response to treatment, but the benefit is lost after several interventions. In light of these factors, not all patients with exacerbations should be treated. We typically reserve therapy for patients with a definite change in functional status, usually related to a significant decline in vision, motor, or cerebellar function.

b. **Therapy.** Acute exacerbations usually are managed with methylprednisolone or corticotropin. There are no definitive data to indicate which drug is more effective. Methylprednisolone is probably superior because it usually is given over a shorter time. The cortisol response to corticotropin is not consistent or may be delayed, and the endogenous steroid production may never reach the range generally recommended for inflammatory autoimmune diseases. The optimal doses and treatment schedules are not well-studied. Most treatment protocols for acute exacerbation call for 25 to 60 units of corticotropin given intramuscularly or infused over 8 hours and tapered gradually over 2 to 4 weeks. Intravenous methylprednisolone may be given in doses of 500 to 1,000 mg each morning for 5 days. This may be followed by prednisone, 60 mg every morning for 3 days, then decreased every 3 days by 10 mg on a relatively rapid taper. The prednisone appears to help prevent immediate relapses after discontinuation of the methylprednisolone.

Exacerbations may be managed with oral prednisone without the preceding methylprednisolone. We are more reluctant to treat patients in this manner because an optic neuritis trial showed benefit from methylprednisolone followed by oral prednisone but increased relapse rates for optic neuritis after treatment with oral prednisone alone. Treatment with glucocorticoids is avoided in the care of pregnant patients. Severe exacerbations in these patients have been managed successfully with plasma exchange in isolated cases. Finally, consideration may be given to intravenous (IV) immune globulin or plasma exchange in the care of patients with fulminate disease for which where glucocorticoids have provided no benefit.

2. **Management of relapsing–remitting disease.** Seven agents are frequently used in the United States to manage relapsing–remitting disease. They are glatiramer acetate (Copaxone), INF *ß*-1b (Betaseron and Extavia), INF *ß*-1a (Avonex and Rebif), fingolimod (FTY720, Gilenya), and natalizumab (Tysabri).

a. **INF-*ß*** has been shown to reduce the number and severity of exacerbations as well as the number of enhancing lesions as detected at cranial MRI. These interferons are INF *ß*-1a (Avonex and Rebif) and INF *ß*-1b (Betaseron and Extavia). They have generally been well-tolerated. The most common side effects are a flu-like syndrome of feeling febrile, usually without and elevated temperature, fatigue, and myalgia during the first weeks to months of therapy. In a small subset of patients treated with the once weekly, IM, INF-*ß*, these side effects persist for years. Switching the patient to a high dose, high frequency, SQ INF-*ß* usually results in immediate resolution of these side effects. This is possibly due to improved tolerization with more frequent administration. Subcutaneous INF-*ß* also causes injection site reactions that can last weeks and usually reoccur as long as the drug is administered. Other side effects include mild lymphopenia and elevation of serum transaminase levels that rarely necessitate withdrawal of treatment. INF *ß*-1a (Avonex) requires weekly IM injections or (Rebif) three times each week subcutaneous injections and INF *ß*-1b, subcutaneous injections every other day. These medications are most efficacious when started early in the management of relapsing–remitting disease. The hope is that they will prevent disease progression as well as exacerbations. The higher dose INF-*ß* are associated with increased neutralizing antibody production, but the clinical effects of these low-affinity antibodies is quite variable and the antibody sometimes disappears with time. In my clinic, neutralizing antibodies are checked in any patient with significant signs of progression or increased MRI activity. Over the years, only 6.6% of these patients have a moderate or high antibody titer. Two trials have compared low-dose INF-*ß* (Avonex) to higher dose INF-*ß* (Rebif and Betaseron). The higher dose interferon was more effective in both trials.

b. **Glatiramer acetate** copolymer 1 (Copaxone) is composed of a random assortment of four amino acids constituting a synthetic polymer. As with INF-*β*, glatiramer acetate is more efficacious administered early in the disease. It is injected daily in a subcutaneous manner. This medication has decreased the exacerbation rate in patients. MRI data were not available from the original study. Extended studies, however, have shown MRI evidence of decreased lesions with use of glatiramer acetate, although the effect seems to be more delayed than with the interferons. Side effects include local injection site reactions and rare transient systemic post injection reactions, including chest pain, flushing, dyspnea, palpitations, and anxiety. No laboratory monitoring is necessary. Trials to compare the efficacy of INF-*β* and glatiramer acetate have shown little difference between the efficacy of the medications. The trials were well-designed, but they did implement the newer McDonald's criteria for diagnosis. All trials to date using these new criteria have shown great efficacy, sometimes several foul when compared with the original pivotal trials. This may be due to the fact that patients diagnosed with these criteria may be selected very early in the disease course and respond better. One must be very careful when making such comparisons across trials but several investigators are suspicious of this data as well as the actual efficacy of multiple newly studied agents using the McDonald's criteria, all showing excellent results.

c. **Natalizumab (Tysabri).** It is an effective treatment for RRMS based on two randomized trials; however, its use has been reserved for patient with RRMS failing to respond to the conventional treatments. Some experts recommend the use of natalizumab as a first line treatment in patients with active disease burden. It is admistered as an IV infusion of 30 mg monthly. The infusion is typically followed by an hour period of observation. Its use has been associated with the development of a rare PML. As of March 31, 2011, approximately 83,300 patients have received natalizumab in the post marketing setting worldwide. The peak incidence of the PML was noted in post marketing data to be between 24 and 36 doses of natalizumab. As of June 1, 2011, there have been 133 confirmed cases of PML worldwide. Based on the 133 cases, the overall risk of PML was estimated to be 1.51 per 1,000 patients; incidence was noted to be higher in patient who were exposed to chemotherapeutic agents prior or during the natalizumab treatment (95% confidence interval: 1.27 to 1.79 per 1,000 patients).

d. **Fingolimod.** In two large controlled trials, fingolimod, a sphingosine analogue, was effective for reducing the relapse rate in patients with RRMS. However, this benefit is associated with an increased risk of life-threatening infections, bradyarrhythmia, and certain cancers.

In late September 2010, the manufacturer received regulatory approval from the FDA for marketing oral fingolimod 0.5 mg daily for the treatment of RRMS. Although there is no consensus yet among experts, the use of fingolimod is likely to be limited in most cases to treat newly diagnosed patients who have active relapsing MS and prefer oral administration despite the increased risks associated with this agent. However, fingolimod may be also be used to treat patients with active RRMS who are intolerant of beta interferons and glatiramer acetate.

The trials of fingolimod excluded patients with diabetes because they readily develop macular edema. As fingolimod also predisposed the patient to macular edema, we suggest not using fingolimod to treat patients with MS who have diabetes.

The most common side effects associated with fingolimod include headache, flu-like symptoms, diarrhea, back pain, elevated liver enzymes, and cough. Less common but potentially serious adverse events associated with fingolimod include bradyarrhythmia and atrioventricular block (potentially fatal), macular edema, diminished respiratory function, and tumor development.

Before starting fingolimod, patients should have the following:

(1) CBC and liver function test (LFT) results within 6 months.
(2) ECG.
(3) Ophthalmologic examination, some experts recommend using objective methods of evaluating the macula (ocular coherence topography), to be repeated at 3 to 6 months intervals.

(4) Varicella serology and varicella zoster virus vaccination if antibody negative for those without a history of chicken pox or prior vaccination; fingolimod should not be started until 1 month after vaccination.
(5) Skin examination at baseline to screen for evidence of precancerous skin lesions.
(6) Pulmonary function tests with spirometry.
(7) Women of childbearing potential should be informed of risk for adverse fetal outcomes (pregnancy class C).

At treatment initiation, baseline pulse and blood pressure should be measured and the patient observed for 6 hours after the first dose for signs of bradycardia or atrioventricular block.

Other agents currently used in the management of RRMS include cyclophosphamide, azathioprine, IV immunoglobulin, and statins given their anti-inflammatory effect.

Corticosteroids combined with other agents:

New agents currently under investigation for the management of RRMS include alumtizumab, daclizumab, fumarate, laquinimod, and teriflunomide.

3. **Management of progressive disease.** With the establishment of progressive disease, patients frequently are more difficult to treat. Clinicians must carefully evaluate whether they are using immune-modulating agents to control fixed lesions with substantial gliosis and scarring or actual active plaques. Because it often is the former, patients typically have little response. Furthermore, the agents used often are so harsh that they may be employed only a short while; however, the disease may still progress for years. In each case, both clinician and patient must carefully weigh the risk-to-benefit ratio and reach full agreement after the patient has been completely informed. The complex nature of choosing these medications for particular disease forms and patients makes it difficult to make prudent decisions without substantial background information and expertise. A clinician specializing in the treatment of patients with MS more optimally makes these decisions.
   a. **Agents under investigation.** Several agents have been evaluated for the management of progressive disease. Azathioprine, cyclophosphamide, and cyclosporine provide benefit to individual patients, but the adverse effects of these agents preclude their use to treat the patient population at large. Methotrexate has shown some promise in the management of primary and secondary progressive MS, and further investigation is merited. INF β-1b has been studied in the management of secondary progressive disease in Europe with excellent results. However, the results were suboptimal when the trial was attempted in the United States. Glatiramer acetate was not effective in the management of primary progressive MS, and INF β-1a (Avonex) offered little benefit in the management of secondary progressive disease.
   b. **Mitoxantrone** has been approved for the management of worsening relapsing–remitting and of primary and secondary progressive disease. It has been shown in trials to reduce relapses and disability as well as development of new enhancing lesions at MRI. The medication is dose limited by it potential to potentiate maligincies and its cardiac toxicity, which is its main adverse affect. This cumulative toxicity limits usage to <3 years. Consequently, this drug is reserved for patients with severe disease that has not resolved with other medications who agree to accept the risk. There is also concern about leukemia that will have to be resolved over time. Because of toxicity, before administration of each dose, left ventricular ejection fraction is measured by means of echocardiography or multiple gated acquisition scanning. Mitoxantrone is typically not given to patients who have received at least 140 mg per m^2, patients with an ejection fraction of <50%, or those in whom a significant reduction in ejection fraction has occurred throughout the course of administration. Mitoxantrone is given as a 5 to 15 minute IV infusion of 12 mg per m^2 every 3 months. Before each administration, left ventricular ejection fraction and a CBC and metabolic profile are obtained. Patients with elevated results of LFTs or an absolute neutrophil count <1,500 cells per mm^3 are excluded. Finally, women of childbearing potential should have negative results of a pregnancy test before each dose.

4. **Future therapies for MS.** There is currently a substantial amount of research involving immune system modifications as therapy for MS. Some of these areas include modification of adhesion molecules, costimulating factors, the trimolecular complex, interferons, phosphodiesterase inhibitors, matrix metalloproteinase inhibitors, nitric oxidase inhibitors, and T REG cells. There is also interest in growth factors, oligodendroglia transplantation, and bone marrow transplantation. It is beyond the scope of this chapter to discuss this research in detail. Through the tremendous efforts by many investigators and participation in clinical trials by many patients, there has been substantial progress in the understanding and management of MS in the last few years. The development of optimal immune-modulating therapies for the future will require the continued collaboration of clinical and laboratory scientists. This is a very exciting and hopeful time in the treatment of patients with MS with several new agents likely to be approved in the next 1 to 2 years.

Recommended Readings

Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging: measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. *Ann Neurol*. 2001;49:290–297.

Costantino CM, Hutton J, Baecher-Allan C, et al. Multiple sclerosis and regulatory T cells. *J Clin Immunol*. 2008;28:697–706.

European Study Group on Interferon ß-1b in Secondary Progressive MS. Placebo-controlled multicenter randomised trial of interferon ß-1b in treatment of secondary progressive multiple sclerosis. *Lancet*. 1998;352:1491–1497.

Frohman EM, Goodin DS, Calabresi PA, et al. The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61:602–611.

Goodin DS, Arnason BG, Coyle PK, et al.; for the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61:1332–1338.

Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS council for clinical practice guidelines. *Neurology*. 2002;58:169–178.

IFNß Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43:655–661.

IFNß Multiple Sclerosis Study Group, University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. *Neurology*. 1995;45:1277–1285.

Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med*. 2000;343:898–904.

Jacobs LD, Cookfair DL, Rudick RA, et al.; for the Multiple Sclerosis Collaborative Research Group (MSCRG). Intramuscular interferon beta-la for disease progression in relapsing multiple sclerosis [published correction appears in *Ann Neurol*. 1996;40:480]. *Ann Neurol*. 1996;39:285–294.

Johnson KP, Brooks BR, Cohen JA, et al.; for the Copolymer 1 Multiple Sclerosis Study Group. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multi-center, double-blind, placebo-controlled trial. *Neurology*. 1995;45:1268–1276.

Johnson KP, Brooks BR, Cohen JA, et al. Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Copolymer 1 Multiple Sclerosis Study Group. *Neurology*. 1998;50:701–708.

Lublin FD, Reingold SC; The National Multiple Sclerosis Society USA Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology*. 1996;46:907–911.

Lucchinetti C, Bruck W, Parisi J, et al. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Ann Neurol*. 2000;47:707–717.

Meinl E, Krumbholz M, Hohlfeld R. B lineage cells in the inflammatory central nervous system environment: migration, maintenance, local antibody production, and therapeutic modulation. *Ann Neurol*. 2006;59:880–892.

Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing-remitting multiple sclerosis. *N Engl J Med*. 2003;348:15–23.

Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. *N Engl J Med*. 2000;343:938–952.

O'Connor PW, Goodman A, Willmer-Hulme AJ, et al. Randomized multicenter trial of natalizumab in acute MS relapses: clinical and MRI effects. *Neurology*. 2004;62:2038–2043.

Paty DW, Li DKB, Duquette P, et al. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis, 2: MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43:662–667.
Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria." *Ann Neurol*. 2005;58:840–846.
PRISMS (Prevention of Relapses and Disability by Interferon beta-la Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1 a in relapsing/remitting multiple sclerosis [published correction appears in *Lancet*. 1999;353:678]. *Lancet*. 1998;352:1498–1504.
Shapiro RT. *Managing the Symptoms of Multiple Sclerosis*. 4th ed. New York, NY: Demos; 2003.
Wolinsky JS. The diagnosis of primary progressive multiple sclerosis. *J Neurol Sci*. 2003;206:145–152.
Zozulya AL, Wiendl H. The role of regulatory T cells in multiple sclerosis. *Nat Clin Pract Neurol*. 2008;4(7):384–398.

CHAPTER

41 Movement Disorders

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Movement disorders can be divided into **hypokinetic** and **hyperkinetic.** Hypokinetic movement disorders refer primarily to disorders with decreased amplitude and/or speed of movement (parkinsonism), whereas hyperkinetic movement disorders are those displaying excess of movement (chorea, dystonia, myoclonus, tics, and tremor).

I. HYPOKINETIC MOVEMENT DISORDERS

A. Parkinson's disease (PD) is the most common cause of degenerative parkinsonism. PD's response to dopaminergic medications is robust, compared with the atypical parkinsonisms (previously referred to as Parkinson-plus syndromes) in which the response, if any, is partial and transient.

1. **Nonpharmacologic management** of PD includes education about the disease, support of patient and family, appropriate nutrition, and exercise. Exercise can improve symptoms and their response to treatment, in addition to reducing fatigue, enhancing sleep, and potentially yielding a disease-modifying effect in the long run. A well-balanced diet is essential for PD patients because of the increased risk of malnutrition and weight loss. Redistribution of dietary protein can be beneficial in the care of patients with advanced PD as protein interferes with absorption of levodopa in the gastrointestinal tract.
2. **Pharmacologic therapy** for PD.
   a. **Neuroprotection.** None of the currently available therapies is firmly acknowledged as disease modifying. The selective monoamine oxidase B (MAO-B) inhibitors selegiline (deprenyl) and rasagiline (Azilect; Teva) have been tested in designs suggestive of such an effect, but their symptomatic benefit may be masking any putative neuroprotective effects. A study testing the potential disease-modifying effect of coenzyme Q10 at a dose of 2,400 mg per day was stopped at an interim analysis for failing to meet a prespecified milestone. Levodopa's introduction in the 1970s dramatically reduced the mortality from this disease, but this effect is believed to result from a purely symptomatic effect.
   b. **Symptomatic management of PD.** Many drugs are useful for improving parkinsonian symptoms. Initiation of PD treatment can be tailored to patients' age, employment status, predominant PD symptoms, severity of illness, intercurrent medical problems, side-effect profile of previous medications, and cost.
      (1) **Selegiline** (Eldepryl; Somerset) and **Rasagiline** (Azilect, TEVA) are irreversible, selective inhibitors of MAO-B at the recommended doses of up to 5 mg twice a day and 1 mg every day, respectively. **Zelapar** (Zydis selegiline; Valeant) is an orally disintegrating formulation of selegiline, taken at 2.5 mg per day.

Adverse effects of selegiline are relatively infrequent when the drug is used early in the disease. Occasional patients report insomnia related to its amphetamine-like metabolite. To minimize insomnia, selegiline should not be used late in the afternoon or evening. Rasagiline, on the other hand, does not produce amphetamine-like metabolites. Although a restricted low-tyramine diet has been recommended by the American Food and Drug Administration to minimize the "cheese effect," such effect is not expected at the recommended doses, designed to maintain selectivity of MAO-B receptors.

Patients taking MAO-B inhibitors should not be given meperidine (Demerol; Sanofi) for pain control or **dextromethorphan.** Although serotonin syndrome has been reported in patients taking selegiline with selective serotonin reuptake inhibitors (SSRIs), many patients are on this combination without adverse effects.

(2) **Amantadine** (Symmetrel; Endo Pharmaceuticals) is used in the management of mild to moderate PD and is most helpful in addressing tremor and levodopa-induced dyskinesias. The various mechanisms of action include *N*-methyl-D-aspartate receptor antagonism, blockade of dopamine reuptake, stimulation of dopamine receptors, and promotion of dopamine release.

Amantadine is excreted unchanged in the urine. The usual dosage range is 100 mg two or three times a day (Table 41.1). Elderly patients and those sensitive to the effects of medications should probably start with 25 mg per day for a few days, using a syrup formulation.

Adverse effects of amantadine may be mild but some are intolerable. The most common are leg edema and **livedo reticularis,** a mottling discoloration of the lower limbs, as well as effects associated with its anticholinergic properties, such as disorientation and hallucinations, as well as dry mouth and blurry vision, especially in older patients.

(3) **Anticholinergic drugs** have been used for many years in the management of PD. Dopamine depletion in the striatum causes a relative "hypercholinergic" state that responds to the use of anticholinergic drugs. Many centrally acting anticholinergic drugs are available, but the two most commonly used in the United States are **trihexyphenidyl** (Artane; Lederle) and **benztropine** (Cogentin; Merck). **Biperiden** (Akineton; Knoll), **orphenadrine** (Norflex; 3M Pharmaceuticals), and **procyclidine** (Kemadrin; GlaxoSmithKline) are rarely used.

Anticholinergics may be used early in the course of PD. Tremor remains the only practical indication for their use given the poor side-effect profile (see below). Typically, **trihexyphenidyl** is started at doses of 1 mg per day and increased weekly up to 2 mg four times per day until symptomatic control is obtained or side effects develop. **Benztropine** usually is started at 0.5 mg per day and titrated up to 4 mg per day. If anticholinergics are to be discontinued, this should be done gradually to avoid withdrawal effects.

Adverse effects of anticholinergic medications include both **peripheral antimuscarinic side effects** (e.g., dry mouth, impaired visual accommodation, urinary retention, constipation, tachycardia, and impaired sweating) and **central effects** (e.g., sedation, dysphoria, memory difficulties, confusion, and hallucinations).

(4) **Dopamine receptor agonists** directly stimulate dopamine receptors. The currently commercially available dopamine agonists in the United States are **pramipexole** (Mirapex; Boehringer-Ingelheim), **ropinirole** (Requip; GlaxoSmithKline), **apomorphine** (Apokyn, Ipsen), and **bromocriptine** (Parlodel; Novartis). The long-acting ergot derivative bromocriptine and cabergoline are rarely used for the treatment of PD. Their use in North America has been largely restricted to the treatment of hyperprolactinemia. The transdermally delivered **rotigotine** (Neupro; UCB/Schwarz Pharma) is temporarily off the market due to the development of crystals in the patch system. **Pergolide** (Permax; Elan) was withdrawn from the US market due to increased risk of cardiac valvulopathy. **Lisuride** and **piribedil** are available in other countries.

Dopamine receptor agonists may relieve all of the cardinal manifestations of PD. Despite the theoretical advantages over levodopa by acting directly on striatal dopamine receptors while circumventing the degenerating dopaminergic neurons, dopamine agonists are less effective than levodopa, yielding a lower risk of **dyskinesia** and **motor fluctuation** compared with it, and have an extensive list of potential side effects. Agonists can be used both as monotherapy and as adjuncts to levodopa. To minimize side effects, the dosage of a dopamine agonist should be increased gradually until the desired effect is obtained. Table 41.1 shows common dosages for different antiparkinsonian drugs. Apomorphine can only be administered subcutaneously as a rescue treatment for intractable and disabling wearing off. An apomorphine challenge is required to determine the correct dose of the drug while the patient is pretreated with an antiemetic, such as **domperidone** or **trimethobenzamide.**

TABLE 41.1 Antiparkinsonian Medications

Drug	Total Daily Dose (mg)	Frequency
Selegiline	5–10	b.i.d. (morning and noon)
Zydis selegiline	1.25–2.5	q.d.
Rasagiline	1	q.d.
Amantadine	200–300	b.i.d.–t.i.d.
Trihexyphenidyl	4–8	b.i.d.–q.i.d.
Benztropine	2–4	b.i.d.–q.i.d.
Levodopa	300–3,000	q.i.d.–q 2 h
Levodopa CR[a]	200–400	q.h.s.
Levodopa + entacapone	200–1,500	t.i.d.–5/d
Clozapine	6–75	q.d.–b.i.d.
Apomorphine	2–8	q.d.–6/d p.r.n.
Bromocriptine	7.5–60	t.i.d.
Pramipexole	1–4.5	t.i.d.
Ropinirole	3–24	t.i.d.
Rotigotine	2–8	q.d.

Bromocriptine is no longer recommended for PD treatment.

Abbreviations: b.i.d., twice a day; q.d., every day; q.i.d., four times a day; t.i.d., three times a day ; q.h., every hour; p.r.n., as needed.

[a]Levodopa CR is no longer recommended for daily use given its unpredictable pharmacokinetic profile. Its use is restricted to bedtime to address nocturnal or early-morning PD symptoms.

Dopaminergic adverse effects of dopamine agonists include **nausea, vomiting, postural hypotension,** and **excessive daytime sleepiness** and **psychiatric manifestations** including visual hallucinations and impulse-control disorders. Elderly and cognitively impaired patients are more prone to psychiatric side effects. Impulse control disorders (excessive shopping, compulsive gambling, and hypersexuality, among others) may develop 20 months after the onset of therapy, which demands regular monitoring. Also in the long term, dopamine agonists can cause **leg edema** and livedo reticularis. Older **ergot-derived dopamine agonists** such as bromocriptine and cabergoline in rare instances cause **pulmonary** and **retroperitoneal fibrosis, cardiac valvulopathy, vasospasm,** and **erythromelalgia** and can exacerbate **angina** and **peptic ulcer disease.**

(5) **Levodopa** is the most effective antiparkinsonian medication. It is mainly absorbed in the proximal small intestine by a carrier-mediated process for neutral amino acids and is similarly transported across the blood–brain barrier. Once in the brain, it is converted to dopamine by the enzyme aminoacid dopa decarboxylase. Levodopa is administered in combination with a peripheral dopa decarboxylase inhibitor (carbidopa in North America or benserazide in Europe). Inhibition of peripheral dopa decarboxylase markedly reduces the required total daily dose of levodopa and minimizes the gastrointestinal side effects and hypotension caused by peripheral conversion of levodopa to dopamine.

Available preparations of levodopa include **immediate-release carbidopa–levodopa** (Sinemet; Dupont), an orally disintegrating tablet (Parcopa; Azur Pharma), and a **controlled-release** preparation (Sinemet CR, Dupont). A minimum of 75 mg per day of carbidopa is required for appropriate peripheral decarboxylation. Carbidopa–levodopa preparations are available as 10 per 100, 25 per 100, and 25 per 250 tablets (carbidopa milligrams per levodopa milligrams) and as 25 per 100 and 50 per 200 tablets in the controlled-release preparation. Sustained-release preparations are 30% less bioavailable and substantially more erratic in its pharmacokinetics than the immediate-release forms. Because of the latter, Sinemet CR is no longer recommended for the control of daytime symptoms, and its use is reserved for reemergence of night-time or early-morning symptoms.

Levodopa generally relieves all of the cardinal signs of PD—bradykinesia, tremor, and rigidity. Delaying levodopa in any patient older than 70 years of age or in younger individuals insufficiently treated with dopamine agonists or MAO-B inhibitors is no longer recommended. Unlike the core deficits of tremor, bradykinesia, and rigidity, axial deficits, such as impaired postural reflexes, hypophonia, and dysphagia, are less reliably improved. A lack of response to levodopa may suggest a diagnosis of one of the atypical parkinsonisms, but an adequate trial with doses up to 1,500 mg of levodopa should be tried before considering anyone nonresponder. Treatment with carbidopa–levodopa usually is initiated using 25 per 100 immediate-release tablets titrating slowly upward to minimize acute side effect.

As the disease progresses, patients may develop motor complications in the form of motor fluctuations with **wearing off** toward the end of a dose cycle (reemergence of parkinsonian deficits or appearance of end-of-dose or early-morning dystonia) or choreic or choreathetoid movements (**dyskinesia**). **Wearing off** can be improved by decreasing the interdose interval of levodopa, increasing the individual levodopa doses, adding a catechol-*O*-methyltransferase (COMT) or MAO-B inhibitor, or considering apomorphine subcutaneous injections. Choreic movements of the upper body predominantly head and neck is often indicative of **peak-dose dyskinesia** and requires lowering the levodopa doses, increasing the interdose interval, or adding amantadine. Choreic movements predominantly of the lower body, especially legs, feet, and pelvis, may occur at the beginning of or at the end of a dose cycle of levodopa and are referred to as **diphasic dyskinesia.** Unlike peak-dose dyskinesias, diphasic dyskinesias are treated by increasing the dose of levodopa or decreasing the interdose interval. In general, motor complications, particularly dyskinesia, begin after 2 to 10 years of levodopa therapy. Younger patients are more prone to dyskinesia and motor fluctuations earlier in the course of the disease. When medication adjustments do not improve these motor complications, deep brain stimulation (DBS) of the subthalamic nucleus (STN) or internal pars of the globus pallidus (GPi) may be considered (see section 3, below).

The short half-life of immediate-release levodopa is believed to be a major factor in the development of motor complications. A gel formulation of levodopa continuously administered intrajejunally is under investigation and expected to become available in the United States in 2012. A similar preparation has been available in Europe for over a decade (**Duodopa;** Abbott).

Adverse effects of levodopa can be classified into acute and chronic. In the short term, **nausea, vomiting,** and hypotension-related lightheadedness can be addressed by adding extra carbidopa (Lodosyn; Bristol-Myers Squibb), 25 to 75 mg three times per day, to enhance the peripheral decarboxylation and minimize bioavailability of dopamine outside the brain, where is typically toxic. Another option is to use a peripheral dopamine receptor blocker such as **domperidone** in doses of 10 to 20 mg three times a day. Domperidone is not currently available in the United States but can be readily obtained from Canadian online pharmacies. In the long term, patients may develop changes in behavioral complications in the form of psychosis, paranoia, sexual preoccupation, impulse control disorder, mania, or agitation. **Visual hallucinations** can be quite vivid in the form of people or animals. Mental status changes usually are dose-dependent and typically lessen with medication reduction, although at the expense of deterioration of motor function. Quetiapine (Seroquel; Astra-Zeneca) or clozapine (Clozaril; Novartis) may be considered in these cases, as the only antipsychotics safe to use in PD. Reports of accelerated melanoma growth in PD patients taking levodopa have been published. However, melanoma seems to be more prevalent among PD patients regardless of their exposure to levodopa or other PD drugs.

(6) **COMT inhibitors** are used as adjuncts to levodopa. By blocking the peripheral conversion of levodopa to 3-*O*-methyldopa, COMT inhibitors increase the bioavailability of levodopa. Two COMT inhibitors are available—**tolcapone** (Tasmar; Valeant) and **entacapone** (Comtan; Novartis). A carbidopa–levodopa–entacapone

preparation (Stalevo; Novartis) is also available. Tolcapone is used in doses of 100 to 200 mg three times a day, and entacapone 200 mg is given with each dose of levodopa up to 2,000 mg per day. If tolcapone is used, liver function tests should be monitored periodically at least for the first 6 months because of earlier reports of rare cases of tolcapone-induced **liver failure,** some fatal. Side effects of COMT inhibitors are related to increased bioavailability of levodopa. In addition, **diarrhea** and a **brownish-orange discoloration of the urine** may occur.

(7) **Visual hallucinations** and **psychosis** are adverse effects that can occur in association with any antiparkinsonian medication. Any potential triggering event, such as infections or metabolic derangements, should be actively sought and treated, if present. Otherwise, decreasing or discontinuing the dose of dopaminergic medications is warranted, in the following order if hallucinations persist: anticholinergics, amantadine, selegiline/rasagiline, and dopamine agonists. If worsening of motor symptoms make such a reduction impossible, the judicious use of one of the safe atypical antipsychotics quetiapine or clozapine, or an acetylcholinesterase inhibitor, such as rivastigmine, may be necessary. **Clozapine** is started at a dose of usually 6.25 mg at bedtime. Because 1% to 2% of patients taking clozapine may experience **agranulocytosis,** patients should be monitored with weekly blood counts. **Quetiapine** is effective in the management of dopaminergic-induced psychosis at doses of 12.5 mg to 300 at night without worsening parkinsonism.

(8) **Constipation** is a common problem among PD patients. Management should include dietary modifications, increasing fluid and fiber intake, exercise, and minimizing or eliminating the use of anticholinergic medications. **Psyllium** (Metamucil; Procter & Gamble) 1 tsp (5 ml) two to four times a day may be added. Osmotic agents such as **sorbitol** and **lactulose** are often helpful. Agents that stimulate intestinal motility such as **bisacodyl** (Dulcolax; Novartis) could be added. Some patients may need enemas.

(9) Other potential problems of patients with PD include **nocturia, urinary urgency and frequency, erectile dysfunction, dysphagia, orthostatic hypotension,** and **sleep problems** (see Chapters 7, 9, 18, and 31). **Depression** requires special mention as it affects about 50% of patients with PD and may respond to antidepressant medications such as SSRIs and SNRIs, given the involvement of serotonin but importantly of norepinephrine in PD.

3. **Surgery.** The stereotactic surgical options to treat PD patients include ablative procedures and **DBS** at different targets—ventral intermediate nucleus of the thalamus (Vim), GPi, and STN. The success of surgical treatment of patients with PD depends on a careful selection of the appropriate candidates. First, only patients with idiopathic PD should be considered. Patients with advanced disease, poor response to levodopa, dementia, uncontrolled depression, uncontrolled hallucinations, and unstable medical problems are unlikely to benefit from these procedures. Surgical candidates should undergo a presurgical neuropsychological evaluation to rule out substantial cognitive dysfunction.

   a. **Thalamotomy** and **thalamic DBS** are procedures directed at managing contralateral medically intractable **tremor** regardless of etiology. Neither of these two procedures improves other features of PD. Tremor reduction occurs in approximately 80% of patients. Bilateral thalamotomy is no longer recommended due to the high risk of dysarthria. Bilateral thalamic DBS may interrupt bilateral thalamic output with fewer side effects than thalamotomy, allowing for adjustment of stimulation to maximize benefits and minimize side effects.

   b. **Pallidotomy** and **pallidal DBS,** targeting the posteroventral GPi, are useful for PD patients with severe dyskinesia and motor fluctuations. Like bilateral thalamotomy, bilateral pallidotomy is no longer recommended due to the high incidence of dysarthria. Improvement in motor function and a marked anti-dyskinetic effect can be striking. PD symptoms that persist during the on state (e.g., freezing and dysarthria) do not respond well to pallidotomy. Improvement in the off-medication state is approximately 30% for pallidotomy and 40% for pallidal DBS.

c. **STN DBS** is currently the preferred surgical procedure for advanced PD with motor fluctuations and dyskinesia. The improvement is mainly during the off state with up to 60% improvement in motor scores reported. DBS may improve the quality of the on state by approximately 10%. STN stimulation allows for a greater reduction of antiparkinsonian medication compared with pallidal stimulation. GPi and STN DBS offer comparative benefits according to a recent head-to-head comparison study.

B. Atypical parkinsonisms are a group of rare degenerative conditions within the akinetic-rigid syndrome to which PD belongs.

1. **Multiple system atrophy (MSA)** is a progressive neurodegenerative disease characterized by a combination of **parkinsonism, cerebellar dysfunction,** and **autonomic failure.** The nomenclature MSA-P and MSA-C are used when parkinsonian or cerebellar features predominate, respectively. The parkinsonism tends to be tremorless. Clinical features that suggest the diagnosis are hyperreflexia or other corticospinal signs, severe early orthostatic hypotension and/or urinary incontinence, atypical levodopa-induced dyskinesias (affecting face [sardonic grin] and feet), Pisa syndrome (lateral truncal deviation), and inspiratory stridor.
   a. Levodopa may provide transient improvement of parkinsonian sympoms albeit rarely sustained beyond 1 year. Other dopaminergic drugs are not indicated.
   b. Orthostatic hypotension may be the greatest source of disability and can be worsened by levodopa. Nonpharmacologic measures include liberalizing salt and water intake, using waist- or thigh-high compressive leg stockings during the day, and raising the head of the bed 8 inches (20 cm) at night to minimize supine hypertension and excessive nocturnal diuresis. Patients should be careful rising from the sitting or supine positions and should avoid heavy meals. When pharmacotherapy is required, the peripheral α-1-adrenergic receptor agonist **midodrine** (ProAmatine; Roberts) may be used, starting at 2.5 mg three times a day, increasing by 2.5-mg weekly increments up to a maximum of 10 mg three times a day When midodrine is insufficient, treatment with the mineralocorticoid **fludrocortisone** (Florinef; Bristol-Myers Squibb) may be added at doses of 0.1 to 0.3 mg per day, as needed. The other potentially useful drugs are methylphenidate, pyridostigmine, erythropoietin, ergots, and desmopressin.
   c. **Urinary frequency** or **incontinence** should be evaluated with the assistance of an urologist. Treatments such as **oxybutynin** (Ditropan; Alza), **solifenacin** (Vesicare; Astellas), **tolterodine** (Detrol; Pfizer), **darifenacin** (Enablex; Novartis), or **trospium chloride** (Sanctura; Esprit) for a spastic bladder or **bethanechol** (Urecholine; Odyssey) for a hypotonic bladder may provide relief. Some patients need intermittent or continuous catheterization. **Sildefanil** (Viagra; Pfizer), **tadalafil** (Cialis; Lilly), and **vardenafil** (Levitra; GlaxoSmithKline) may be useful for management of erectile dysfunction.
   d. Dysarthria and dysphagia may benefit from evaluation by a speech therapist. Some patients with severe dysphagia need percutaneous gastrostomy. Gait difficulties and instability may necessitate use of supportive devices and physical therapy. Patients with MSA and inspiratory stridor should undergo a sleep study to determine whether concurrent obstructive sleep apnea requires treatment.
2. **Progressive supranuclear palsy (PSP)** is an atypical parkinsonism characterized by early postural instability and falls, disproportionate neck rigidity (sometimes with retrocollis), facial dystonia, supranuclear vertical gaze abnormalities, pseudobulbar affect, subcortical frontal dementia, and apathy.
   a. **Management** of PSP is extremely limited. Antiparkinsonian medications are rarely helpful, although a trial of levodopa is prudent.
   b. Symptomatic palliative therapies for PSP include management of dysarthria and dysphagia with the assistance of a speech therapist and may include the use of a gastrostomy tube among other measures. Because of the significantly decreased blinking rate, patients with PSP are at increased risk of keratitis and should use artificial tears. Blepharospasm and neck dystonia can be managed with botulinum toxin injections. Depression and emotional incontinence can be managed with antidepressants. Dystonia may benefit from amantadine. Gait instability can be managed with physical therapy and supportive devices.

II. HYPERKINETIC MOVEMENT DISORDERS

A. Chorea is an involuntary movement disorder characterized by irregular, dance-like jerky movements occurring within or between body parts in a random sequence. It can result from a variety of disorders of the basal ganglia.

1. **Huntington's disease (HD)** is an autosomal-dominant degenerative brain disorder characterized by the insidious development of motor, cognitive, and psychiatric symptoms progressing toward death on average of about 20 years after onset of symptoms. The underlying genetic defect is the expansion of a CAG trinucleotide repeat of the HD gene, the product of which is a protein called **huntingtin.** Symptomatic treatment is directed at the major clinical features of the disease.
   a. Choreiform movements can be reliably controlled with **neuroleptics** that have potent postsynaptic dopamine blocking effects such as haloperidol (Haldol; Ortho-McNeil). Benzodiazepines such as lorazepam and clonazepam may also decrease chorea. **Tetrabenazine** (Xenazine; Lundbeck), a reversible dopamine depleter and mild postsynaptic dopamine blocker, is effective in reducing chorea. Effective doses range from 12.5 to 50 mg three times a day.
   b. **Depression** affects at least 30% to 50% of patients with HD. In HD patients, the suicide rate is four to eight times greater than in the general population. Depression can be managed with all standard agents used for the management of major depression. **SSRIs** typically are the drugs of choice for HD. **Mirtazapine** (Remeron; Organon) can be helpful in the care of HD patients with cachexia, anxiety, and insomnia because it can increase body weight and assist in sleep induction.
   c. **Irritability and aggressive behavior** are common psychiatric manifestations in HD. Propranolol, valproic acid, and carbamazepine are potentially useful to treat aggressive behavior related to frustration and impatience.
   d. **Mania** and **hypomania** can occur in HD. Approximately 10% of HD patients may exhibit hypomanic behavior. Mania in HD responds better to carbamazepine and oxcarbazepine than to lithium. Other therapeutic alternatives are valproic acid and clonazepam.
   e. **Psychosis** has an estimated frequency of 3% to 25% among patients with HD and is more common among patients with early-onset disease. Atypical antipsychotic agents such as **clozapine, quetiapine, olanzapine,** and **risperidone** are effective in controlling psychotic symptoms. These drugs are associated with increased risk of hyperglycemia and diabetes.
2. Other causes of chorea include neurodegenerative disorders (e.g., chorea-acanthocytosis, Wilson's disease (WD), and dentatorubropallidoluysian atrophy), Sydenham's chorea, systemic lupus erythematosus, hyperthyroidism, and drug-induced chorea (e.g., phenytoin, oral contraceptives, stimulants, or antiparkinsonian drugs). Regardless of the underlying cause, the movements can be improved with the use of neuroleptics. However, disease-specific treatments should be pursued as appropriate (e.g., warfarin in antiphospholipid antibody syndrome, penicillin in Sydenham's chorea). The risk of tardive dyskinesia (TD) is uncertain when neuroleptics are used in the treatment of chorea.
3. **Hemiballismus** is a severe form of chorea, with violent, flailing movements of the proximal aspect of the limbs on one side of the body. It is classically caused by lesions in the **contralateral** STN, but lesions outside the STN are more common. Treatment includes supportive care, prevention of self-injury, and pharmacologic agents such as benzodiazepines, neuroleptics, and catecholamine-depleting agents (reserpine or tetrabenazine). Valproic acid and other gamma-aminobutyric acid (GABA)-ergic drugs may be alternative therapeutic options. Surgical alternatives exist for patients who do not appropriately respond to medical therapy.

B. Tics are common movement disorders, affecting as many as 20% of children. They are brief, rapid, purposeless, repetitive movements involving one or more muscular groups. They are differentiated from other paroxysmal movement disorders by their partial voluntary control with suppressability when performing complex tasks, premonitory "urge," and stereotypic appearance.

1. **Tourette's syndrome (TS)** is a childhood-onset neuropsychiatric disorder characterized by motor and phonic tics. Tics wax and wane and tend to improve considerably

during adulthood. **Obsessive–compulsive behavior** and **attention deficit disorder (ADD)** are comorbid conditions frequently associated with TS and may be more disabling than tics themselves.

a. **Tics** do not require treatment unless they are troublesome to the patient. The first step in treatment is education and reassurance. If further intervention is needed, **clonidine** (Catapres; Boehringer-Ingelheim) starting at 0.05 mg at bedtime and increased 0.05 mg every few days can be considered. The efficacy of clonidine for tic control is modest, however. **Guanfacine** starting at 0.5 to 1 mg at bedtime is another option that may be less sedating than clonidine.

Neuroleptics are the most efficacious agents for tic suppression. **Haloperidol** (Haldol, McNeil Laboratories) is probably the most commonly used neuroleptic for tics. **Pimozide** (Orap; Gate) was developed specifically for use in TS and may cause less sedation than haloperidol does. Pimozide may prolong the QT interval. Other neuroleptics such as **trifluoperazine** (Stelazine; GlaxoSmithKline) and **thiothixene** (Navane; Pfizer) can also be helpful. Atypical antipsychotics such as **risperidone** (Risperdal; Janssen), **ziprasidone** (Geodon; Pfizer), **aripripazole** (Abilify; Otsuka), and **olanzapine** (Zyprexa; Lilly) are being used with increasing frequency, though data from controlled trials are lacking. The necessary dosage can vary widely among patients and at different times for a given patient, given the fluctuating severity of the natural history of tics. Sedation and depression may be troublesome side effects. Although the risk of TD appears to be low among patients with TS, this potential long-term adverse effect must be discussed with patients and documented in the medical record. **Clonazepam** (Klonopin; Roche) and baclofen may be helpful to some patients. Botulinum toxin injections may be helpful for some tics.

b. Management of **obsessive–compulsive behavior** associated with TS is identical to that of the purely psychiatric condition. SSRIs and clomipramine (Anafranil; Novartis, may be used in this regard. The major adverse effects of clomipramine are sedation and anticholinergic effects.

c. **ADD** and other behavioral disorders of children may be difficult to control. Clonidine, tricyclic antidepressants, or selegiline may be effective. Use of CNS stimulants such as **methylphenidate** (Ritalin; Novartis) may ease ADD. **Modafinil** (Provigil; Cephalon) may be useful as well. The diverse behavioral abnormalities sometimes exhibited by children with TS not infrequently necessitate family counseling and other nonpharmacologic approaches.

C. Myoclonus is a shock-like, brief, involuntary movement caused by muscular contraction (positive myoclonus) or muscular inhibition (negative myoclonus). Myoclonus can originate from the cortex, subcortical areas, brainstem, or spinal cord. Common causes of myoclonus include metabolic derangements, such as renal and hepatic failure, and epileptiform disorders.

1. **Diagnosis** should include a thorough history and physical examination plus blood glucose and electrolytes, drug and toxin screen, renal and hepatic function tests, brain imaging, and EEG. A search for inborn errors of metabolism and paraneoplastic antibodies may be indicated in some cases.
2. The ideal therapy for myoclonus is to manage the underlying condition. However, symptomatic treatment should be used if treatment is likely to make a significant functional impact (Table 41.2). **Clonazepam** at 2 to 6 mg per day, **valproic acid** 250 to 1,500 mg per day, **levetiracetam** (Keppra; UCB) 500 to 4,000 mg per day, and **piracetam** up to 24 g per day (not available in the United States) are first-line drugs for the management of myoclonus. **Acetazolamide, zonisamide, primidone, 5-hydroxytryptophan,** and **tetrabenazine** can also be helpful. Many patients need polytherapy to control myoclonus.

D. TD is a generic term used to describe persistent involuntary movements that occur as a consequence of long-term treatment with dopamine receptor antagonists (neuroleptics). Antipsychotics are the main causative group of neuroleptics, but antiemetics such as metoclopramide, prochlorperazine, and promethazine may also behave as TD-causing neuroleptics. The risk factors for development of classic TD include old age, female gender, mood disorder, and "organic" brain dysfunction. Classic TD usually consists of

TABLE 41.2 Medications Used in the Management of Myoclonus

Drugs	Total Daily Dose (mg)	Frequency
Usually helpful drugs		
Clonazepam	0.5–20	b.i.d.–t.i.d.
Valproic acid	250–2,500	b.i.d.–q.i.d.
Piracetam	1,000–24,000	t.i.d.
Levetiracetam	500–3,000	b.i.d.–t.i.d.
Zonisamide	100–600	q.d.–b.i.d.
Primidone	125–1,500	b.i.d.–t.i.d.
5-Hydroxytryptophan (with carbidopa)	100–3,000	q.i.d.
Occasionally helpful drugs		
Trihexyphenidyl	1–60	t.i.d.
Methysergide	1–8	q.d.
Propranolol	40–240	b.i.d.–t.i.d.
Fluoxetine	20–60	q.d.

oral–buccal–lingual dyskinesia that may be associated with a variety of repetitive limb or trunk stereotyped movements.

1. The pathophysiologic mechanism of TD is not completely understood, but it is thought to be related to an increased number and affinity of postsynaptic D2 dopamine receptors in the striatum. The patient's condition may initially improve after the neuroleptic agent is restarted or after the dosage is increased. Unfortunately, this is likely to perpetuate the problem.
2. The ideal management of TD would be prevention of this condition by avoiding unnecessary use of neuroleptics and using the minimally effective dose. Anticholinergic medications can worsen classic TD.
   a. **Dopamine depleters** such as **reserpine** or **tetrabenazine** have been among the most useful medications to treat TD. Dosages of reserpine usually are started at 0.10 to 0.25 mg three times a day and may be gradually increased to 3 to 5 mg per day. Reserpine may cause parkinsonism, depression, orthostatic hypotension, and peptic ulcer disease. Tetrabenazine can be started at 25 mg per day and gradually increased up to 150 mg per day in divided doses. The most common limiting side effects are sedation, depression, and parkinsonism.
   b. **Benzodiazepines** may prove useful for patients with mild symptoms. Long-acting agents such as clonazepam (usually 1.5 to 3 mg per day) provide the most consistent relief of symptoms.
   c. **Branched-chain amino acids** (Tarvil; SHS North America) have been shown to significantly decrease TD symptoms in males. It is used at a dose of 222 mg per kg three times a day.
   d. **Neuroleptics,** used in the lowest possible dosages, may be necessary if symptoms markedly interfere with activities of daily living.
   e. **Tardive dystonia** is a subtype of TD that typically affects younger people. It usually involves the neck and trunk muscles. Management of tardive dystonia differs from that of classic TD in that anticholinergics are potentially beneficial, and botulinum toxin can be used in focal or segmental forms. Dopamine depleters are also useful.
   f. For many patients, combination therapy is most effective. The use of a benzodiazepine with either a dopamine depleter or a low dosage of an atypical neuroleptic may be necessary. Vitamin E might prevent further deterioration of TD, but it is not really clear if it can improve TD symptoms. The eventual rate of remission is approximately 60% and improvement is slow, taking as long as 2 years.

E. Dystonia is a syndrome of sustained muscle contraction causing abnormal repetitive movements, twisting, or abnormal postures. Up to 21 different types of dystonia so far can be differentiated genetically and are designated as DYT1 to 21. Idiopathic dystonia can be generalized or restricted to a particular muscle group. With the exception of DYT3 (X-linked Lubag disease), patients with primary idiopathic dystonia have

no gross or microscopic abnormalities. Secondary dystonia includes several inherited inborn errors of metabolism such as dopa-responsive dystonia (DRD or DYT5) and WD. Trauma, vascular disease, space-occupying lesions, drugs, and toxins are other causes of secondary dystonia.

1. **DRD** or **DYT5** is an autosomal dominant disorder caused by a mutation in the GTP cyclohydrolase I gene. It usually becomes apparent during childhood with a gait disorder, foot cramping, or toe walking. It can involve the trunk and arms and can be misdiagnosed as cerebral palsy. Patients with this form of dystonia have few symptoms after first awakening but the symptoms progress throughout the day. This disorder is exquisitely sensitive to small doses of levodopa (50 to 200 mg). A brief trial of levodopa for childhood-onset dystonia is frequently recommended to exclude DRD.
2. Medical management of dystonia of any cause can be attempted with the medications listed in Table 41.3. None of these medications provides complete relief of symptoms. Combinations of medications can be beneficial. Extremely high doses of anticholinergic drugs such as trihexyphenidyl have been reported to benefit more than 50% of patients in some trials (sometimes at doses greater than 100 mg per day). Therapy usually is started with 1 mg per day and increased 1 to 2 mg per week divided on a three times a day schedule until control of symptoms is achieved or intolerable adverse effects appear. The combination of a dopamine depleter such as reserpine, an anticholinergic, and a postsynaptic dopamine blocker may be beneficial to patients with severe dystonia. GPi DBS can be offered to patients to with pharmacologically intractable and disabling dystonia.
3. Injection of **botulinum toxin** is the first line of treatment of many patients with focal and segmental dystonia. There are seven botulinum toxin serotypes, but only types A and B are available in the United States—**botulinum toxin type A** (onabotulinumtoxinA [Botox; Allergan], abobotulinumtoxinA [Dysport; Ipsen], and incobotulinumtoxinA [Xeomin, Merz]) and **botulinum toxin type B** (rimabotulinumtoxinB [MyoBloc; Solstice]). The toxin is injected directly into the affected muscle, producing reversible pharmacologic denervation. Injections usually are repeated at an average interval of 12 to 16 weeks when toxin type A or B are used. Potential side effects include excessive transient weakness of the injected and adjacent muscles, dry mouth, and local hematoma.

F. **Tremor** is probably the most common movement disorder. It is an involuntary, rhythmic oscillation of a body part.

1. **Essential tremor (ET)** typically includes both postural and kinetic tremor. A positive family history of tremor is common among ET patients. Tremor typically may improve with small amounts of alcohol. Generally, it is not possible to completely eliminate the tremor, and the goal of therapy should be to normalize activities of daily living.

TABLE 41.3 Medications Used in the Management of Dystonia

Class	Example	Dosage
Anticholinergics	Trihexyphenidyl	6–100 mg/d
Dopaminergics	Levodopa	50–300 mg/d
	Bromocriptine	7.5–40 mg/d
Antidopaminergics	Haloperidol	2–20 mg/d
Benzodiazepines	Diazepam	5–20 mg/d
	Clonazepam	1–10 mg/d
GABA agonists	Baclofen	15–240 mg/d
Antidepressants	Amitriptyline	25–150 mg/d
Anticonvulsants	Carbamazepine	300–1,200 mg/d
	Valproic acid	500–1,500 mg/d
Dopamine depleters	Reserpine	0.5–5 mg/d
	Tetrabenazine	50–300 mg/d
Toxins	Botulinum toxin type A (Botox)	Up to 400 MU

Abbreviation: MU, mouse units.

TABLE 41.4 Medications Used in the Management of Tremor

Drug	Dose (mg)	Frequency
Propranolol	60–800	b.i.d.–q.i.d.
Propranolol LA	80–320	q.d.
Atenolol	50–150	q.d.
Nadolol	120–240	q.d.
Sotalol	75–200	b.i.d.
Primidone	50–750	q.d.–t.i.d.
Alprazolam	0.125–3	b.i.d.–q.i.d.
Clonazepam	0.5–6	t.i.d.
Topiramate	100–400	q.d.–b.i.d.
Gabapentin	1,200–1,800	t.i.d
Nimodipine	120	q.–4 hr

One-half to two-thirds of patients with ET benefit from pharmacologic therapy (Table 41.4). In some cases, the tremor may be quite refractory, and surgical treatment should be considered.

a. ***ß*-Adrenergic receptor antagonists** are used most extensively to manage ET. The clinical response to *ß*-blockers is variable and usually incomplete. These drugs reduce tremor amplitude but not tremor frequency and appear to be less effective in managing voice and head tremor. Nonselective *ß*-blockers such as **propranolol** (Inderal; Wyeth-Ayerst) are preferred. Propranolol should be started at small doses (e.g., 10 mg three times a day) and titrated upward as needed. Doses larger than 320 mg per day usually do not confer additional benefit. Potential side effects of *ß*-blockers include congestive heart failure, second- or third-degree atrioventricular block, worsening of obstructive lung disease, and masking of signs of hypoglycemia. The *ß*-blockers can also cause fatigue, nausea, diarrhea, rash, erectile dysfunction, and depression. **Nadolol** (Corgard; Bristol-Myers Squibb) is an option if propranolol causes CNS side effects as this drug does not readily cross the blood–brain barrier. **Atenolol** (Tenormin; Astra Zeneca), **sotalol** (Betapace; Bayer Healthcare), **metoprolol** (Lopressor; Novartis), and **timolol** (Blocadren; Merck) are potentially useful in the treatment of ET.

b. **Primidone** (Mysoline; Xcel) may improve ET. The mechanism of action of primidone for management of tremor is unknown. Primidone decreases the amplitude of tremor but does not alter its frequency. Treatment usually is started at 25 mg at bedtime, and a response may begin at doses between 50 and 350 mg per day. Doses up to 750 mg per day divided three times a day may be required for benefits to appear. Side effects include vertigo, nausea, unsteadiness, and drowsiness.

c. **Benzodiazepines** may be used if the above drugs do not provide sufficient control of symptoms. Long-acting agents such as **clonazepam** can be used, but some patients may respond better to the use of a shorter-acting agent such as **alprazolam** (Xanax; Pfizer). Clonazepam at 1 to 3 mg per day can be very effective in orthostatic tremor. Potential adverse effects include sedation, ataxia, tolerance, and potential for abuse.

d. **Botulinum toxin injections** of limb tremor in ET may offer modest improvement of tremor that might be more cosmetic than functional as no improvement has been seen in functional scales. Transient weakness is the most common side effect.

e. **Other drugs** that may be considered for the management of ET are **gabapentin** (Neurontin; Pfizer), **topiramate** (Topamax; Ortho-McNeil), and **zonisamide** (Zonegran; Eisai). **Clozapine**) may also improve ET; however, the potential risk of idiosyncratic agranulocytosis makes this option unappealing.

f. **Surgery** can be used in selected cases when activities of daily living are severely affected despite medical management. Stereotactic thalamotomy or Vim DBS improve contralateral tremor.

G. WD is an autosomal recessive disorder of copper accumulation caused by a defect in copper excretion into the bile. Low-plasma levels of **ceruloplasmin** characterize WD.

Copper deposits typically occur in the liver, iris, and basal ganglia. Other organs may be affected as well. A variety of movement disorders can accompany WD, including tremor, dystonia, chorea, dysphagia, dysarthria, and parkinsonism. Symptomatic management of the movement disorder is as discussed in other sections of this chapter.

1. **Recommended screening** methods for patients with a neurologic signs and symptoms of WD are as follows:
   a. **Serum ceruloplasmin** and **slit-lamp examination** for **Kayser–Fleischer's (KF) rings.** Approximately 90% of WD patients who have neurologic symptoms have a low-ceruloplasmin level. KF rings are present in 99.9% of WD patients who have neurologic symptoms.
   b. **24-hour urine copper.** In patients with neurologic WD, the 24-hour urine copper level is always more than 100 μg before chelation treatment. This value may be falsely elevated in patients with long-standing liver disease.
2. Copper-rich foods such as shellfish, chocolate, liver, nuts, and soy products should be avoided. However, this is not sufficient to avoid further accumulation, and **zinc acetate** is used to block mucosal absorption of copper. Zinc acetate is taken at a dose of 50 mg three times a day between meals. The toxicity of zinc is negligible, although it can cause abdominal discomfort. Zinc is the drug of choice for maintenance therapy after chelation and in presymptomatic or pregnant patients.
3. **Penicillamine** (Cuprimine; Aton) acts by means of reductive chelation of copper. It mobilizes large amounts of copper, mainly from the liver. The standard dose after a titration phase is 250 mg four times a day, each dose separated from food. Doses up to 1,500 mg per day can be used. Several potentially serious adverse effects are associated with penicillamine. Approximately 50% of patients treated with penicillamine have **marked neurologic deterioration,** and half of these patients do not recover to the pre-penicillamine level of function. Approximately one third of patients who start taking penicillamine have an **acute hypersensitivity reaction.** Other subacute potential toxicities include **bone marrow suppression,** membranous glomerulopathy, myasthenia gravis, reduced immune response, hepatitis, pemphigus, and a lupus erythematosus-like syndrome with a positive antinuclear antibody. A CBC with platelets and urinalysis are recommended every 2 weeks for the first 6 months of therapy and monthly thereafter.
4. **Trientine** (Syprine; Aton) is a chelating agent that induces urinary excretion of copper and has a more favorable side-effect profile than penicillamine, with a lower risk of neurological deterioration (25%), which makes it more favorable for consideration as initial WD treatment. Dosage and administration are identical to those of penicillamine. Although trientine promotes less copper excretion than does penicillamine, it does not cause a hypersensitivity reaction. The other toxicities are somewhat similar to those of penicillamine but less frequent.
5. **Tetrathiomolybdate** is an experimental drug that prevents absorption of copper from the intestine and is absorbed into the blood, where it binds to copper to form nontoxic complexes. It has been used successfully at a dose of 120 mg per day to manage acute WD with neurologic manifestations.
6. **Liver transplantation** is curative of WD.

Recommended Readings

Axer H, Axer M, Sauer H, Witte OW, Hagemann G. Falls and gait disorders in geriatric neurology. *Clin Neurol Neurosurg.* 2010;112(4):265–274.

Espay AJ. Management of motor complications in Parkinson disease: current and emerging therapies. *Neurol Clin.* 2010;28(4):913–925.

Factor SA, Molho ES. Emergency department presentations of patients with Parkinson's disease. *Am J Emerg Med.* 2000;18(2):209–215.

Klein C, Schneider SA, Lang AE. Hereditary parkinsonism: Parkinson disease look-alikes—an algorithm for clinicians to "PARK" genes and beyond. *Mov Disord.* 2009;24(14):2042–2058.

Kleiner-Fisman G, Herzog J, Fisman DN, et al. Subthalamic nucleus deep brain stimulation: summary and metaanalysis of outcomes. *Mov Disord.* 2006;21(suppl 14):S290–S304.

Lang AE. When and how should treatment be started in Parkinson disease? *Neurology*. 2009;72(7, suppl):S39–S43.
Louis ED. Essential tremors: a family of neurodegenerative disorders? *Arch Neurol*. 2009;66(10):1202–1208.
Moro E, Lang AE, et al. Criteria for deep-brain stimulation in Parkinson's disease: review and analysis. *Expert Rev Neurother*. 2006;6(11):1695–1705.
Ozelius LJ, Bressman SB. Genetic and clinical features of primary torsion dystonia. *Neurobiol Dis*. 2011;42(2):127–135.
Pahwa R, Factor SA, Lyons KE, et al. Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66(7):983–995
Poston KL, Frucht SJ. Movement disorder emergencies. *J Neurol*. 2008;255(suppl 4):2–13.
Postuma RB, Lang AE. Hemiballism: Revisiting a classic disorder. Lancet Neurol 2003;2(11):661-8.

CHAPTER

42 Dementia

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Dementia is defined as a decline in memory and at least one other cognitive function that impairs the patient's ability to function in activities of daily living. Behavioral abnormalities are common and contribute to functional impairment. Neurodegenerative processes, particularly Alzheimer's disease (AD), account for more than 90% of dementia cases. Therapeutic aims are to identify the few patients with reversible etiologic factors and palliate disabling symptoms for as long as possible, while the condition, inevitably, will eventually worsen.

I. DEMENTIA (REVERSIBLE CAUSES)

The percentage of patients with dementia having reversible underlying etiologic factors is relatively small (2% to 3%). However, as many as 40% of patients with no reversible etiologic factors have treatable conditions, the correction of which can improve temporarily the patient's ability to function.

A. Structural lesions causing dementia. Space-occupying masses or abnormalities in brain structure for which the patient can be treated may be identified with brain imaging studies, including CT, MRI, single photon emission computed tomography, and positron emission tomography. Unfortunately, neurosurgical intervention in many of these patients can halt deterioration but not greatly improve clinical symptoms.

1. **Normal pressure hydrocephalus.** Patients with gait abnormalities, urinary incontinence, dementia, and ventricular enlargement out of proportion to sulci on CT and MRI images should be referred for neurosurgical evaluation and possible placement of a ventriculoperitoneal shunt. Patients whose symptoms improve after lumbar puncture are particularly likely to improve after shunting. Gait and incontinence are more likely to improve than is memory. Overall, one-third of patients improve, one-third remain unchanged, and one-third have progressive symptoms.
2. **Subdural hematoma and hygroma.** Chronic subdural hematoma and hygroma can be asymptomatic or cause cognitive impairment or frank dementia in the elderly. Neurosurgical evaluation is required. Increases in the size of the fluid collection and progressive clinical impairment are indications for surgical intervention. Surgery often does not improve cognition but stops progression of cognitive impairment.
3. **Frontal, temporal, and parietal lobe tumors.** Large meningiomas, gliomas, and metastases to the brain that occupy substantial space or cause marked edema in the adjacent frontal, temporal, or parietal lobe can cause dementia. Patients with such tumors should be treated by means of neurosurgical excision or by biopsy and radiation therapy or chemotherapy, as appropriate for the tumor type and location. Among patients older than 65 years, the prognosis for meaningful recovery from cognitive impairment and clinical dysfunction after such treatments is guarded.
4. **Closed head injuries,** even mild injuries or injuries involving rapid acceleration or deceleration of the brain without an actual blow to the head can produce a subsequent postconcussive syndrome characterized by impaired memory, concentration, and processing speed; affective symptoms such as irritability, depression, or anxiety; and somatic symptoms including headache, dizziness, nausea, fatigue, disturbed sleep, blurred vision, tinnitus, photophobia, or phonophobia. The severity of the initial head injury does not necessarily correlate with the severity of the postconcussive symptoms. The mechanism of injury is thought to be diffuse axonal injury through axonal shearing, especially in the frontal lobes. Treatment is pharmacological and rehabilitative treatment of the symptoms while avoiding further injury.

B. Metabolic and nutritional abnormalities associated with dementia. Relatively subtle deviations from the normal ranges for laboratory parameters can cause or significantly exacerbate mental impairment in elderly patients. A history of fluctuating cognitive deficits suggests a metabolic cause of dementia. Changes in mental status often are reversible with correction of the metabolic disturbance or nutritional deficiency.

1. **Hyponatremia and hypernatremia.** Hypernatremia is most common in association with dehydration and may be found in physically impaired patients who are dependent on caregivers for their oral intake. For dehydrated patients, both free water and electrolytic deficits should be calculated and corrected, and body weight and electrolytes should be measured frequently and adjusted as necessary. Relatively minor hyponatremia with serum sodium (Na^+) at 120 to 130 mg per dl can significantly impair cognition in the elderly. Correction of hyponatremia can totally reverse mental impairment. Hyponatremia with Na^+ <120 mg per dl should be corrected over 3 or more days because overrapid normalization can precipitate CNS demyelination.
2. **Hypocalcemia and hypercalcemia.** Abnormalities in serum calcium levels can be associated with hypoparathyroidism or hyperparathyroidism, antihypertensive therapy, cancer, and renal disease. The underlying cause should be determined and managed.
3. **Hypoglycemia and hyperglycemia.** Many patients with diabetes mellitus have dementia with varying degrees of reversibility. The long-term effects of diabetes mellitus can contribute to both microvascular disease and accelerate atherosclerosis in the major vessels supplying the brain. Both can cause vascular dementia. Many patients with diabetes have very high-blood glucose levels (>300 to 400 mg per dl) and variable changes in mental status during the day. These changes may be difficult to recognize and treat. Similarly, some patients may have periods of confusion associated with unrecognized hypoglycemia. Management of glucose abnormalities requires careful monitoring of blood glucose levels and correction by adjustments in diet and in dosages of oral hypoglycemic agents, or by means of insulin injections as necessary to achieve normal blood glucose levels.
4. **Cobalamin (vitamin B_{12}) deficiency.** Chronic serum levels of cobalamin of 200 pg per ml or lower can be associated with various hematological, gastrointestinal, and neurological abnormalities. Typical reversible neuropsychiatric deficits that can be seen with B_{12} deficiency include psychotic symptoms and deficits in concentration and visuospatial and executive function.

C. Endocrine abnormalities that cause dementia. Chronic endocrine diseases can cause cognitive impairment in elderly persons with few other physical findings associated with hormonal deficiency or excess. Detection and correction of these conditions can lead to complete reversal of dementia, including return to normal activities of daily living.

1. **Thyroid disease.**
   a. **Hypothyroidism.** In the elderly, hypothyroidism should be managed initially with levothyroxine (T_4) at a dosage of 0.025 mg per day. The dosage may be increased in 0.025 mg increments at monthly intervals, with routine monitoring of T_4 and thyroid-stimulating hormone levels. The dose should be increased until symptoms improve and until T_4 levels are in the therapeutic range. If the initial T_4 thyroid level is very low in an elderly patient, supplemental steroids, such as prednisone at 5.0 to 7.5 mg per day, may be given for the first 2 weeks after levothyroxine is initiated.
   b. **Hyperthyroidism.** An endocrinologist should generally be consulted and appropriate therapy begun, including propranolol to decrease pulse rate and anxiety, medical therapy with methimazole or with radioactive iodine, or surgical excision of the thyroid gland. Most mental status changes associated with thyroid disease are reversible.
2. **Diabetes mellitus.** See **I.B.4.**
3. **Hypoparathyroidism and hyperparathyroidism.** See **I.B.3.**

D. Dementia secondary to systemic organ failure. The CNS depends on normal functioning of all of the major organ systems. Mild abnormalities in systemic organ functions in an elderly patient can cause mental status changes including confusion, disorientation, and memory loss.

1. **Pulmonary disease.** Both acute illnesses (such as pneumonia) and chronic obstructive pulmonary disease can cause hypoxemia resulting in dementia. Supplemental oxygen

administered by nasal cannula or face mask can improve cognitive function. Various diseases of the lungs, particularly small-cell cancer, can metastasize or have distant effects on the brain and cause dementia. The underlying tumor should be the focus of treatment.

2. **Hepatic disease.** Diseases of the liver, such as hepatitis and cirrhosis, can cause dementia. The dementia is often associated with elevated blood ammonia levels. The underlying liver disease is the focus of treatment. Cognitive improvement results from lowering ammonia levels with lactulose, rifaxamin, or both.
3. **Cardiac disease.** Cardiac dysfunction can impair cognitive functioning in different ways. Congestive heart failure can decrease the blood supply to the brain. Enlarged heart chambers and valvular disease can promote formation of thrombi that can embolize to the brain. Arrhythmias may decrease blood flow to the brain. Management of the underlying cardiac disease should be the focus.
4. **Renal disease.** Chronic or acute renal failure can cause uremic encephalopathy. Dialysis and transplantation have decreased the frequency of this illness. Patients with renal disease are more prone to fluctuating changes in mental status resulting from a variety of metabolic abnormalities.

E. **Autoimmune disorders.** Several autoimmune disorders have been found to cause progressive deterioration of mental function. Paraneoplastic antibodies such as ANNA-1 (Hu), Ma2, CRMP, and voltage-gated potassium channel (VGKC) antibodies may occur in individuals with cancers. These antibodies have been associated most often with cancers of the lung, but have also been described with numerous other neoplasms; in other patients, especially with VGKC antibodies, no tumor is found. Treatment consists of identifying and treating the associated cancer and administering high-dose corticosteroids; additional immunological therapy such as intravenous immune globulin or plasma exchange, or other immunosuppressants may be needed. Other steroid-responsive encephalopathies include Hashimoto's encephalopathy, which is associated with thyroglobulin or thyroid peroxidase antibodies, and other nonvasculitic autoimmune inflammatory meningoencephalitides in which no specific autoantibody is identified. Impaired mental status can also be seen in individuals with connective tissue disorders such as systemic lupus erythematosus or Sjögren's syndrome; the underlying condition should be treated.

F. **Infections.** Either systemic or CNS infections may cause changes in mental status, particularly in the elderly.

1. **Systemic infections.** Infectious diseases that cause systemic illness often directly or indirectly affect CNS function. In elderly patients, urinary tract infections and upper respiratory infections can secondarily cause declines in cognitive function that clear after effective antibiotic treatment.
2. **Chronic CNS infections.** Chronic meningitis or encephalitis can be caused by syphilis, tuberculosis, cryptococcus and other fungal infections, or Whipple's disease. Symptoms include intermittent fevers, night sweats, headache, stiff neck, papilledema, nuchal rigidity, rapidly progressive dementia, ataxia, and urinary incontinence (see Chapter 2). Therapy should be appropriate to the identified causative organism. Dementia can occur with HIV infection. These patients are also at higher risk of contracting subacute or chronic meningitis, progressive multifocal leukoencephalopathy (caused by the JC virus), toxoplasmosis, or cytomegalovirus, which can cause cognitive decline. Dementia also occurs among patients who have had herpes simplex encephalitis. Deficits may gradually improve, although some patients may have permanent cognitive loss. Creutzfeldt–Jakob's disease is an irreversible transmissible prion-based dementia that is usually sporadic, although it can also be contracted through exposure to nervous system tissue or fluid from an infected person. The typical clinical course is rapid cognitive decline with myoclonus, or cerebellar signs and gait difficulties that progress to death in 3 to 6 months.

G. **Neurosarcoidosis.** Approximately 5% of individuals with sarcoidosis will experience neurological complications; of these, one-third will have more than one neurologic symptom. Mental status impairment can result from vasculitis, hydrocephalus, aseptic meningitis, parenchymal mass lesions, seizures, or hormonal or metabolic derangements secondary to granulomatous involvement of the hypothalamus or pituitary.

H. Epilepsy (partial complex status epilepticus). Intermittent confusion, staring spells, lip smacking, and automatisms suggest the possibility of intermittent partial status epilepticus. Ictal activity should be demonstrated with EEG. Lorazepam or diazepam should be given for acute suppression of seizures. Anticonvulsants should be used long term for management of the seizure disorder.

I. Side effects of medications taken by the elderly for chronic illnesses. As many as 75% of elderly patients take three or more medications, many of which have the potential to cause side effects of chronic confusion and deficits in cognition and memory. The worst offenders are anticholinergic drugs such as scopolamine and oxybutynin, antihypertensives, antidepressants, anxiolytics, and antipsychotic medications. Anticonvulsants, sleep medications, and analgesics also frequently cause impairment in mental function. Excessive dosages and numbers of medications are probably the most common reversible causes of dementia among the elderly. Medications should be titrated to the lowest dosage levels sufficient for the control of symptoms. Medications that are not clearly effective should be eliminated.

II. DEMENTIA (IRREVERSIBLE CAUSES)

Most patients with dementia have underlying etiologic factors that are not reversible. Therapeutic strategies for irreversible dementia have focused on the prevention of factors contributing to progression and the use of medications to improve symptoms of memory loss, other deficits in cognition, mood disorders, and behavioral disturbances.

A. Neurodegenerative dementias.

1. AD is the most common form of neurodegenerative dementia, accounting for at least 6% of dementia cases. Short-term memory loss is seen early in the course of the disease; other deficits such as disorientation, aphasia, apraxia, agnosia, and executive dysfunction gradually develop over time and lead to loss of ability to function independently. The average course of the illness from diagnosis to death is 4 to 8 years.
   a. **Treatment of cognitive deficits.** Two classes of drugs are approved for the treatment of AD in the United States: cholinesterase inhibitors (ChEIs), and *N*-methyl-D-aspartate (NMDA) receptor antagonists. ChEIs increase acetylcholine at the synapse by slowing the hydrolysis of acetylcholine, and produce modest improvements in cognition and behavioral and psychiatric abnormalities in some patients with AD. Peripheral and central cholinergic side effects can be seen with treatment with this class of drugs. The most common adverse symptoms are dyspepsia, nausea, vomiting, and diarrhea. Leg cramps, vivid dreams, dizziness, headache, or rhinorrhea may also occur. Side effects are more likely when medications are started and at dose escalations. Tolerability can be improved by administration with food or by slowing titration. NMDA receptor antagonists are thought to exert their effects by modulating inappropriate calcium influx into resting neurons, thus reducing "background noise" and improving the chance of generation of action potentials when the neuron is activated. The most common side effects are headache, dizziness, constipation, and confusion. These can be reduced by slowing the rate of titration or decreasing the dose.
      (1) **Donepezil,** a selective acetylcholinesterase inhibitor, is dosed once a day. The initial dose is 5 mg per day. This is increased to 10 mg per day after 4 weeks. Moderate to severe stage patients after 3 months on 10 mg per day may be further increased to 23 mg per day.
      (2) **Rivastigmine,** an acetyl- and butyrylcholinesterase inhibitor, was recently made available as a transdermal patch. The initial dose is one 4.6 mg per 24 hour patch daily for 1 month, then 9.5 mg per 24 hours daily thereafter.
      (3) **Galantamine,** an acetylcholinesterase inhibitor that also modulates nicotinic receptors, is administered once daily in a controlled-release capsule after breakfast each day, beginning with a daily dose of 8 mg. This is titrated to 16 mg per day after 4 weeks and can be further increased to 24 mg a day in another 4 weeks, as tolerated.

(4) **Memantine,** a partial NMDA antagonist, is approved for moderate to severe AD and is most often used in combination with a ChEI. It is initiated at 5 mg daily and increased by 5 mg at 1 week intervals to the target dose of 10 mg twice daily.

b. **Management of behavioral symptoms.** The management of agitation, depression, anxiety, and sleep disorders for patients with dementia can be challenging. Drugs that improve behavioral symptoms can worsen dementia. Some drugs that improve behavioral symptoms in younger patients without dementia may have paradoxical effects in dementia patients. However, dosage ranges that provide effective control of behavioral symptoms vary widely in individual patients, so frequent adjustments in therapy may be necessary to control such symptoms. In general, dosage should be started low, and the rate of increase should be slow.

(1) **Agitation, hallucinations, delusions, and bizarre or violent behavior.** Precipitants of abnormal behaviors, such as environment change, pain, or infection, should be identified and modified, if possible. If nonpharmacologic therapies are unsuccessful, medications may be employed. Trazodone at a dosage of 50 to 200 mg before bedtime can be used for agitation. The atypical neuroleptic drugs may be useful in small doses. These drugs do carry "black box" warnings regarding an increased risk of mortality, mainly from pulmonary and cardiac causes, and caregivers should be made aware of this before therapy is instituted. Target behavioral symptoms for potential improvement should be identified before beginning therapy. Treatment can start with risperidone 0.5 mg, olanzapine 2.5 mg, or quetiapine 12.5 mg, as necessary, with frequency from once per day at night up to three or four times a day. The dosages can be adjusted upward as necessary to control agitation and downward as necessary to minimize side effects. Behavior can actually worsen if the doses are too high. Abnormal behavior becomes progressively more common as dementia worsens, eventually occurring in most patients with AD.

(2) **Depression.** Symptoms of depression present in at least 25% of patients with AD and can occur at any stage of the illness. Therapy for depression can improve cognitive function; therefore, aggressive management is warranted. The selective serotonin reuptake inhibitors (SSRIs) such as sertraline, citalopram, or escitalopram are useful in the treatment of depression in the elderly dementia population because they carry relatively low risk of side effects. These drugs often are effective in lower dosages than those used to treat younger adults. For this reason, treatment should be initiated at one-half of the usual starting dose. Atypical antidepressants such as venlafaxine, bupropion, or duloxetine may also give good results, especially if SSRIs fail. Mirtazapine is another useful antidepressant, if stimulation of appetite is desired; it should be remembered that this medication is sedating at doses below 30 mg per day and activating at doses above 30 mg daily.

(3) **Anxiety, phobias, and excessive motor activities.** When caregivers of patients with dementia describe symptoms suggestive of anxiety, phobias, or excessive motor activities (e.g., constant pacing and hand washing), several questions should be asked. Is this behavior disturbing to the patient? Is it interfering with the patient's function in activities of daily living? Are these behavioral symptoms making it difficult for the caregiver to manage the patient? Small doses of atypical neuroleptics given either as needed or at the time of day that the behavior usually occurs are generally effective. Small doses of a benzodiazepine such as lorazepam at a dose of 0.5 to 1.0 mg or alprazolam at a dose of 0.25 to 0.5 mg may also be useful in managing these symptoms. In the care of patients with dementia, however, these drugs can be excessively sedating, and there is an increased risk of falling. SSRIs may also be helpful, especially for irritability or obsessive–compulsive behaviors.

(4) **Insomnia.** A patient with dementia who is active in the middle of the night puts extraordinary stress on the caregiver. Daytime napping should be discouraged, and lighting should be kept bright during the daytime. If the patient is taking donepezil at bedtime, dosing should be moved to the morning.

Atypical neuroleptics given at bedtime often are helpful. Some patients have responded to melatonin, 3 to 10 mg at bedtime. Diphenhydramine (25 to 50 mg) may also be useful.

2. **Dementia with Lewy's bodies** (DLB) is a spectrum of disorders that includes Lewy's body disease, Parkinson's dementia, and the Lewy's body variant of AD. It is the second most common neurodegenerative dementia, accounting for up to 20% of cases. Clinical features may include progressive dementia with deficits in attention, executive function, and visuospatial function in the early stages and impaired memory later in the course of the illness; cognitive fluctuations that may mimic delirium; parkinsonism; hallucinations, particularly visual; rapid eye movement sleep behavior disorder; autonomic instability; and severe sensitivity/intolerance to neuroleptic medications. Double-blind, placebo-controlled studies of rivastigmine, as well as open-label studies of other ChEIs have shown that these medications are frequently efficatious not only for the cognitive symptoms, but also the psychotic symptoms of DLB.
3. **Frontotemporal dementias** (FTDs) are diagnosed in approximately 5% of patients with dementia. Symptoms may overlap those of AD, but presenting symptoms are often abnormalities of behavior or language, with memory impairment occurring later in the course of the illness. Anecdotal evidence and small studies have suggested that memantine may be helpful in FTD; the evidence for the use of ChEIs is less clear. Treatment of mood and behavioral symptoms is similar to that of AD.
4. **Multiple sclerosis** (MS) produces frank dementia in < 5% of individuals with the condition, but cognitive symptoms are common, occurring in 40% to 70%. The severity of the symptoms correlates roughly with the plaque burden and the degree of callosum atrophy on MRI. Some studies have found that treatment with ß-interferon reduces the progression of cognitive decline.
5. **Other neurodegenerative diseases** that are associated with impaired cognition included Huntington's disease, Wilson's disease, multiple systems atrophy, corticobasal degeneration (CBD), and progressive supranuclear palsy (PSP). These disorders produce subcortical dementias, typified by impaired executive functioning, sequencing, mental flexibility, abstraction, and judgment. Patients with CBD also characteristically have asymmetric limb apraxia that can be severe enough to cause the more-affected limb to engage in seemingly purposeful movements over which the patient has no voluntary control, the so-called alien limb phenomenon, whereas patients with PSP may exhibit echolalia or palilalia.

B. **Vascular dementia.** Accurate diagnosis is important for determining the cause and preventing or delaying progression of the disease.

1. **Subcortical vascular dementia** (previously known as Binswanger's disease) may be the principal cause of symptoms in 5% to 15% of patients with dementia and may occur jointly with AD in another 10%. Control of hypertension, blood sugar, and use of antiplatelet agents may help prevent progression of dementia in patients with multiple infarctions. In patients with elevated levels of cholesterol and triglycerides, reduction should be encouraged by exercise, changes in diet, and administration of a cholesterol-lowering medication. A trial of a ChEI may be useful in those patients who are having ongoing (rather than stepwise) decline, suggesting that there may be concomitant AD pathology.
2. **Multiple infarctions secondary to emboli.** Dementia can occur after repeated embolic strokes. Treatment involves stopping or decreasing frequency of new infarctions, identifying the embolic source, and instituting appropriate therapy. Carotid source embolization can be managed medically with platelet antiaggregants or, if there is more than 50% stenosis, surgically with carotid endarterectomy. Cardiac source emboli usually necessitate long-term anticoagulation. If the cause is infective endocarditis, the patient should not be given anticoagulants, but antimicrobial therapy should target the underlying infection.
3. **Cerebral amyloid angiopathy** is suggested by intermittent parenchymal hemorrhage of the brain. Angiography shows no evidence of aneurysm or arteriovenous malformation. In a small number of these cases with a positive family history, the cause is hereditary cerebral hemorrhage with amyloidosis of the Dutch type or hereditary cerebral hemorrhage with amyloidosis in Icelandic kindred. There is no

treatment but aspirin, and *nonsteroidal anti-inflammatory drugs should be specifically avoided.*

4. **Vasculitis.** The diagnosis of vasculitis is suggested in patients with dementia with diffuse brain disease when there is elevation of the Westergren sedimentation rate to >75 mm per hour without another identified cause and elevation of CSF protein level to >75 mg per dl with fewer than 10 cells per mm^3. Angiography shows characteristic areas of narrowing in the small vessels, which confirms the diagnosis. Patients with vasculitis should be treated aggressively with high-dose intravenous steroids followed by tapering oral steroid therapy. Steroid therapy may improve memory and cognitive deficits dramatically.
5. **Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).** Individuals with a strong personal and family history of migraine and strokes in the third or fourth decade of life should be investigated for CADASIL, an autosomal-dominant disorder caused by a mutation in the notch 3 gene on the short arm of chromosome 19 that causes dysfunction of the smooth muscle of the arterioles of the white matter. Affected individuals typically suffer migraines, strokes beginning in their 30s, mood and behavior changes, and cognitive decline. The most common inherited vascular dementia, it is treated by vigorous management of any associated vascular risk factors and symptomatic treatment.
6. **Emotional incontinence in vascular dementia.** Many patients with multiple infarcts in the frontal lobes interrupting frontal lobe tracts may exhibit characteristic verbal outbursts triggered by even the most minor emotional stimulus. These emotional verbal outbursts may have characteristics of both crying and laughter. They are involuntary and can be very disturbing to patients and their families, often leading to avoidance of social activities. SSRIs or low doses of tricyclic antidepressants can be effective in controlling these symptoms. In addition, a combination medication of dextromethorphan HBr and quinidine sulfate has been recently approved for pseudobulbar affect; however, the populations tested were subjects with MS and amyotrophic lateral sclerosis, and the medication has not yet been shown to be safe or effective for emotional lability seen in dementia. Furthermore, it should be used with caution in individuals with heart failure or who are on serotonergic medications, and it can prolong the QT interval and produce anticholinergic effects.

ACKNOWLEDGMENT

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Recommended Readings

Alzheimer's Association. 2011 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2011;7:208–244.

American Psychiatric Association. Dementia of the Alzheimer's type. In: *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed., text rev. Washington, DC: American Psychiatric Association; 2000.

Ballard C, Day S, Sharp S, et al. Neuropsychiatric symptoms in dementia: importance and treatment considerations. *Int Rev Psychiatry.* 2008;20:396–404.

Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev.* 2006;25:CD005593.

Boeve B. A review of the non-Alzheimer dementias. *J Clin Psychiatry.* 2006;67:1985–2001.

Dodel R, Csoti I, Ebersbach G, et al. Lewy body dementia and Parkinson's disease with dementia. *J Neurol* 2008;255(suppl)5:39–47.

Filippi M, Rocca MA, Benedict RHB, et al. The contribution of MRI in assessing cognitive impairment in multiple sclerosis. *Neurology.* 2010;75:2121–2128.

Gauthier S, Cummings J, Ballard C, et al. Management of behavioral problems in Alzheimer's disease. *Int Psychogeriatr.* 2010;22:346–372.

Helzner EP, Scarmeas N, Cosentino S, et al. Survival in Alzheimer disease: a multiethnic, population-based study of incident cases. *Neurology.* 2008;71:1489–1495.

Kabasakalian A, Finney GR. Reversible dementias. *Int Rev Neurobiol.* 2009;84:283–302.

Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia. An evidence-based review. Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology.* 2001;56:1143–1153.

Maruta J, Lee SW, Jacobs EF, Ghajar J. A unified science of concussion. *Ann N Y Acad Sci.* 2010;1208;58–66.
McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies. Third report of the DLB consortium. *Neurology.* 2005;65:1863–1872.
Rosser MN, Fox NC, Mummery CJ, et al. The diagnosis of young-onset dementia. *Lancet Neurol.* 2010;9:793–806.
Stern BJ. Neurological complications of sarcoidosis. *Curr Opin Neurol.* 2004;17:311–316.
Vernino S, Geschwind M, Boeve B. Autoimmune encephalopathies. *Neurologist.* 2007;13:140–147.
Wilkins CH, Mathews J, Sheline YI. Late life depression with cognitive impairment: evaluation and treatment. *Clin Interv Aging.* 2009;4:51–57.

CHAPTER

43 Central Nervous System Infections

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I. BACTERIAL MENINGITIS

The initial signs and symptoms of bacterial meningitis are fever, stiff neck, headache, lethargy, confusion or coma, nausea and vomiting, and photophobia. Examination of the CSF shows an elevated opening pressure (>180 mm H_2O), a decreased glucose concentration (<40 mg per dl), polymorphonuclear pleocytosis, and an elevated protein concentration. The diagnosis is made by demonstrating the organism with Gram's stain or in culture. Polymerase chain reaction (PCR) to detect bacterial nucleic acid in CSF is available at some centers. *Bacterial meningitis is a neurologic emergency*, and initial treatment is empiric until a specific organism is identified.

A. Therapeutic approach

1. **Dexamethasone therapy.** The American Academy of Pediatrics recommends consideration of dexamethasone in the treatment of infants and children 2 months of age and older with proven or suspected bacterial meningitis on the basis of findings on CSF examination, a Gram's-stained smear of the CSF, or antigen test results. Dexamethasone is also recommended in adults with suspected bacterial meningitis and in proven pneumococcal meningitis (based on CSF gram-positive diplococci or blood or CSF cultures that are positive for *Streptococcus pneumoniae*). In clinical trials, dexamethasone improves the outcome of meningitis. In experimental models of bacterial meningitis, dexamethasone inhibits synthesis of the inflammatory cytokines, decreases leakage of serum proteins into the CSF, minimizes damage to the blood–brain barrier (BBB), and decreases CSF outflow resistance. Dexamethasone also decreases brain edema and intracranial pressure (ICP).

   The recommended dosage of dexamethasone is 0.15 mg per kg intravenous (IV) every 6 hours for the first 4 days of therapy. The initial dose of dexamethasone should be given before or at least with the initial dose of antimicrobial therapy for maximum benefit. Dexamethasone is not likely to be of much benefit if started >24 hours or more after antimicrobial therapy has been initiated. The concomitant use of an histamine-2 receptor antagonist is recommended with dexamethasone to avoid gastrointestinal bleeding.
2. **Antimicrobial therapy.** If bacterial meningitis is suspected, antimicrobial therapy must be initiated immediately. This should be done before the performance of CT or lumbar puncture. Initial antimicrobial therapy is empiric and is determined by the most likely meningeal pathogen according to the patient's age and underlying condition or predisposing factors.
   a. The most likely etiologic organisms of bacterial meningitis in **neonates** are group B streptococci, enteric gram-negative bacilli (*Escherichia coli*), and *Listeria monocytogenes*. Empiric therapy for bacterial meningitis in a neonate should include a combination of ampicillin and either a third or fourth generation cephalosporin (cefotaxime or cefepime).
   b. Empiric therapy for community-acquired bacterial meningitis in **infants and children** should include coverage for *S.pneumoniae* and *Neisseria meningitidis*. A third or fourth generation cephalosporin (ceftriaxone, cefotaxime, or cefepime) and vancomycin are recommended as initial therapy for bacterial meningitis in children in whom the etiologic agent has not been identified. Cefuroxime, also a third-generation cephalosporin, is not recommended for therapy for bacterial meningitis in children because of reports of delayed sterilization of CSF cultures associated with hearing loss in children treated with cefuroxime.

c. Empiric therapy for community-acquired bacterial meningitis in **adults** (15 to 50 years of age) should include coverage for *S. pneumoniae* and *N. meningitidis.* A third-generation cephalosporin (ceftriaxone or cefotaxime) or a fourth-generation cephalosporin (cefepime) plus vancomycin is recommended for empiric therapy. All CSF isolates of pneumococci and meningococci should be tested for antimicrobial susceptibility. Cefotaxime, ceftriaxone, or cefepime is recommended for relatively resistant strains of pneumococci (penicillin minimal inhibitory concentrations [MIC], 0.1 to 1.0 μg per ml and MICs of cefotaxime or cefepime ≤0.5 μg per ml). For highly penicillin-resistant pneumococcal meningitis (MIC > 1.0 μg per ml), a combination of vancomycin and a third-generation or fourth-generation cephalosporin is recommended. Penicillin G or ampicillin can be used for meningococcal meningitis.

d. Initial therapy for meningitis in **postneurosurgical patients** should be directed against gram-negative bacilli, *Pseudomonas aeruginosa*, and *Staphylococcus aureus.* Ceftazidime or meropenem is recommended for management of gram-negative bacillary meningitis in neurosurgical patients. Ceftazidime is the only cephalosporin with sufficient activity against *P. aeruginosa* in the CNS. Vancomycin should be added until infection with staphylococci is excluded.

e. In infants, children, and adults with **CSF ventriculoperitoneal shunt infections,** initial therapy for meningitis should include coverage for coagulase-negative staphylococci and *S. aureus.* The assumption can be made that the organism will be resistant to methicillin; therefore, initial therapy for a shunt infection should include IV vancomycin. Intrashunt or intraventricular vancomycin may also be needed to eradicate the infection.

f. In **immunocompromised patients,** the infecting organism can be predicted on the basis of the type of immune abnormality. In patients with neutropenia, initial therapy for bacterial meningitis should include coverage for *L. monocytogenes,* staphylococci, and enteric gram-negative bacilli. Patients with defective humoral immunity and those who have undergone splenectomy are unable to mount an antibody response to a bacterial infection or to control an infection caused by encapsulated bacteria. These patients are at particular risk of meningitis caused by *S. pneumoniae, Haemophilus influenzae* type b (Hib), and *N. meningitidis.*

g. The most common organisms causing meningitis in the **older adult** (50 years or older) are *S. pneumoniae* and enteric gram-negative bacilli; however, meningitis caused by *Listeria* organisms and Hib are increasingly recognized. The recommended initial therapy for meningitis in the older adult is either ceftriaxone, cefotaxime, or cefepime in combination with vancomycin and ampicillin. Table 43.1 lists empiric antimicrobial therapy for bacterial meningitis by age group. Tables 43.2 and 43.3 list the recommended antimicrobial therapy for bacterial meningitis in neonates, infants and children, and adults by meningeal pathogen.

TABLE 43.1 Empiric Antimicrobial Therapy for Bacterial Meningitis

Age Group	Antimicrobial Agent
Neonates	Ampicillin plus cefotaxime or cefepime
Infants and children	Ceftriaxone, cefotaxime, or cefepime plus vancomycin
Adults (15–50 y)	
Community acquired	Ceftriaxone, cefotaxime, or cefepime plus vancomycin
Otitis, mastoiditis, sinusitis	Ceftriaxone plus vancomycin plus metronidazole
Postneurosurgical	Ceftazidime or meropenem plus vancomycin
Immunocompromised	Ceftazidime or meropenem plus ampicillin
Older adults	Ceftriaxone, cefotaxime, or cefepime plus vancomycin plus ampicillin

TABLE 43.2 Recommended Antimicrobial Therapy for Bacterial Meningitis in Neonates, Infants and Children by Organism

Total Daily Dose

Organism	Neonates (<1 wk)	Neonates (1–4 wk)	Infants and Children (>4 wk)
Hib	Cefotaxime 100 mg/kg a day q12h or Cefepime 100 mg/kg a day q12h	Cefotaxime 150–200 mg/kg a day q8h or cefepime 100 mg/kg a day q12h	Ceftriaxone 100 mg/kg a day IV in a once or twice daily dosing regimen, or cefotaxime 225 mg/kg a day IV in divided doses q6h or cefepime 150 mg/kg a day in divided doses q8h
S. pneumoniae[a]	Cefotaxime	Cefotaxime	Ceftriaxone or cefotaxime or cefepime
Group B streptococci	Ampicillin 100–150 mg/kg a day q8h	Ampicillin 200 mg/kg a day q8h	Ampicillin 200–300 mg/kg a day q4–6h
L. monocytogenes[b]	Ampicillin with or without gentamicin 5 mg/kg a day q8h	Ampicillin with or without gentamicin 7.5 mg/kg a day q8h	Ampicillin with or without gentamicin 5 mg/kg a day q8h
N. meningitidis	Penicillin G 50,000–150,000 U/kg a day q8h, or ampicillin 100–150 mg/kg a day q12h	Penicillin G 150,000–200,000 U/kg a day q6h, or ampicillin 200 mg/kg a day q8h	Penicillin G 250,000–400,000 U/kg a day q4h, or ampicillin IV in divided doses q4–6h
Enteric gram-negative bacilli[a]	Cefotaxime or cefepime	Cefotaxime or cefepime	Ceftriaxone or cefotaxime or cefepime
S. aureus	Oxacillin 50–100 mg/kg a day q6h	Oxacillin 100–200 mg/kg a day q6h	Oxacillin 200–300 mg/kg a day q4h
Methicillin-resistant staphylococci	Vancomycin 20–30 mg/kg a day q12h	Vancomycin 40 mg/kg a day q6h	Vancomycin 40–60 mg/kg a day q6h, may also add intrashunt or intraventricular vancomycin 10 mg once a day

[a]Dosages are the same as for Hib.

[b]Dosages are the same as for group B streptococci.

TABLE 43.3 Recommended Antimicrobial Therapy for Bacterial Meningitis in Adults by Organism

Organism	Antimicrobial Agent
S. pneumoniae	Ceftriaxone 4 g/d (q12h) or cefotaxime 12 g/d (q4h) or cefepime 6 g/d (q8h) plus vancomycin 45–60 mg/kg/d (q6–12h)
N. meningitidis	Penicillin G 20–24 miU/kg a day (q4h) or ampicillin 12 g/d (q4h)
Gram-negative bacilli (except *P. aeruginosa*)	Ceftriaxone 4 g/d (q12h) or cefotaxime 12 g/d (q4h) or cefepime 6 g/d (q8h)
P. aeruginosa	Ceftazidime 8 g/d (q8h) or meropenem 6 g/d (q8h)
H. influenzae type b	Ceftriaxone or cefotaxime or cefepime
S. aureus (methicillin-sensitive)	Oxacillin 9–12 g/d (q4h) or nafcillin 12 g/d (q4h)
Staphylococcus aureus (methicillin-resistant)	Vancomycin 45–60 mg/kg/d (q6–12h)
L. monocytogenes	Ampicillin 12 g/d (q4h) with or without gentamicin
Enterobacteriaceae	Ceftriaxone or cefotaxime or cefepime

3. **Management of increased ICP.** Increased ICP is an expected complication of bacterial meningitis and should be anticipated.
   a. **Elevation of the head of the bed** 30°.
   b. **Hyperventilation** to maintain $PaCO_2$ between 30 and 35 mm Hg.
   c. **Mannitol.**
      (1) **Children.** 0.5 to 2.0 g per kg infused over 30 minutes and repeated as necessary.
      (2) **Adults.** 1.0 g per kg bolus injection and then 0.25 g per kg every 2 to 3 hours. A dose of 0.25 g per kg appears as effective as a dose of 1.0 g per kg in lowering ICP. The main exception is that the higher dose has a longer duration of action. Serum osmolarity should not be allowed to rise above 320 mOsm per kg.
   d. **Pentobarbital.**
      (1) **Loading dose.** 10 mg per kg over 30 minutes.
      (2) 5 mg/kg/hour for 3 hours, supplemented with 200-mg IV boluses until a burst-suppression pattern is obtained on an EEG.
      (3) **Maintenance dosage.** 1 mg/kg/hour by constant IV infusion.
4. **Seizure activity** is such a common complication of bacterial meningitis in adults, especially pneumococcal meningitis, which prophylactic anticonvulsant therapy is not unreasonable.
   a. **Prophylactic therapy.** Phenytoin is administered at a dosage of 18 to 20 mg per kg at a rate no faster than 50 mg per minute. Propylene glycol, the diluent of IV phenytoin, can cause bradycardia, hypotension, and cardiac dysrhythmias. IV phenytoin should be administered via central access while the ECG and BP are monitored. If these side effects are observed, the rate of administration should be decreased. It is recommended that phenytoin be administered no faster than 25 mg per minute in the elderly.

      Fosphenytoin, the prodrug to phenytoin, is administered at a dosage of 18 to 20 mg pulmonary embolism (PE) per kg at a rate no faster than 150 mg per minute. IV fosphenytoin does not contain propylene glycol and thus can be administered at a faster rate. A standard maintenance dosage is 100 mg of phenytoin or 100 mg PE of fosphenytoin every 8 hours. A serum concentration of 10 to 20 μg per ml should be maintained.

      Levetiracetam is an alternative option for parenteral seizure prophylaxis therapy. The loading dose is 1,000 to 1,500 mg intravenously, followed by a maintenance dose of 500 mg every 12 hours. Levetiracetam dosing should be adjusted for creatinine clearance.
   b. **Status epilepticus.**
      (1) **Lorazepam** (0.1 mg/kg for adults; 0.05 mg/kg/dose for children) or diazepam (5 to 10 mg for adults; 0.2 to 0.3 mg/kg/dose for children) is administered IV.

(2) **Phenytoin** is administered in a dose of 18 to 20 mg per kg as described in **I.A.4.a.** Fosphenytoin is administered in a dose of 20 mg PE per kg as described in **I.A.4.a.** If seizures are not controlled, a repeat bolus of 10 mg PE per kg fosphenytoin or 500 mg phenytoin can be given.

(3) If phenytoin fails to control seizure activity, phenobarbital is administered intravenously at a rate of 100 mg per minute to a loading dose of 20 mg per kg. The loading dose of phenobarbital for children is also 20 mg per kg. The most common adverse effects of phenobarbital loading are hypotension and respiratory depression. Before phenobarbital loading, ensure that an endotracheal tube has been placed and mechanical ventilation begun. The primary reason for failure to control seizure activity is either that anticonvulsants are administered in subtherapeutic dosages or, as is the case for phenobarbital, the rate of administration is too slow.

(4) For more information on the management of refractory status epilepticus see Chapters 38, 39, and 58.

5. **Fluid management.** Most children with bacterial meningitis have hyponatremia (serum sodium concentration <135 mEq per L) at the time of admission. For this reason, fluid restriction to correct the serum sodium level is important, but this must be done taking into consideration the adverse effects of hypovolemia on cerebral perfusion pressure. The recommended initial rate of IV fluid administration is approximately three-fourths normal maintenance requirements, or approximately 1,000 to 2,000 ml/m^2/day. A 5% dextrose solution with one-fourth to one-half normal saline solution and 20 to 40 mEq per L potassium is recommended. The volume of fluids administered can be gradually increased when serum sodium concentration increases to >135 mEq per L.

B. Expected outcome. Despite appropriate antimicrobial therapy, patients with bacterial meningitis are very sick. Prognosis depends on age, underlying or associated conditions, time from onset of illness to institution of appropriate antimicrobial therapy, the infecting organism, and the development of brain edema, coma, arterial and venous cerebrovascular complications, hydrocephalus or seizures. Pneumococcal meningitis has the worst prognosis, and a poor prognosis is associated with the extremes of age.

C. Prevention.

1. Rifampin or ciprofloxacin is recommended for all close contacts with a patient who has **meningococcal meningitis.** Rifampin is given in divided doses at 12-hour intervals for 2 days as follows: adults, 600 mg; children, 10 mg per kg; neonates (younger than 1 month), 5 mg per kg. It should not be given during pregnancy. Pregnant and lactating women may be given intravenous or IV ceftriaxone (a single injection of 250 mg).

   The Advisory Committee on Immunization Practices recommends that adolescents and college freshmen be vaccinated against meningococcal meningitis with the tetravalent (Men A,C,W135,Y) meningococcal polysaccharide vaccine.

2. The vaccination of infants with the Hib conjugate vaccine has greatly decreased the incidence of **Hib.** Rifampin prophylaxis should be given to children younger than 4 years of age who have not been fully vaccinated against Hib disease who come in contact with a patient with Hib meningitis. It is recommended for all adults who have close contact with the patient and for the patient, because the organism usually is not eradicated from the nasopharynx with systemic antimicrobial therapy. Rifampin in the following dosages is recommended: adults, 20 mg per kg a day orally for 4 days; children, 20 mg per kg a day orally (maximum 600 mg per day) for 4 days; and neonates (younger than 1 month), 10 mg per kg a day for 4 days. Rifampin is not recommended for pregnant women.

II. HERPES ENCEPHALITIS

Encephalitis is inflammation of the brain parenchyma. Herpes simplex virus (HSV-1) is the principal cause of herpes encephalitis. Initial infection occurs either after

exposure to infected saliva or respiratory secretions, the virus gaining access to the CNS along the olfactory nerve and tract into the limbic lobe, or as a result of reactivation of latent virus from the trigeminal ganglion. Virus is transmitted from infected persons to other persons only through close personal contact. The typical clinical presentation is a several-day history of fever and headache followed by memory loss, confusion, olfactory hallucinations, and seizures. The hallmark sign is a focal neurologic deficit suggestive of a structural lesion in the frontotemporal area. The EEG often is abnormal, demonstrating periodic sharp-wave complexes from one or both temporal regions. The abnormalities on the EEG arise from one temporal lobe initially but typically spread to the contralateral temporal lobe over a period of 6 to 10 days. On CT scans, there is a low-density lesion within the temporal lobe with mass effect. On MRI, the infection appears as an area of high signal intensity on T2-weighted (Fig. 43.1) and fluid-attenuated inversion recovery images. Examination of the CSF shows a lymphocytic pleocytosis (with an average WBC count of 50 to 500 cells per mm^3), elevation in protein concentration, and normal or mildly decreased glucose concentration. CSF should be sent for the PCR assay to detect nucleic acid of HSV-1 and it should be examined for HSV-1 antibodies. Antibodies to HSV-1 do not appear in the CSF until approximately 8 to 12 days after symptom onset, and increase significantly during the first 2 to 4 weeks of infection. In order to determine if there is an intrathecal synthesis of antibodies against HSV-1, send CSF and serum samples. A serum:CSF ratio of <20:1 is considered diagnostic of HSV-1 infection. Because this infection produces

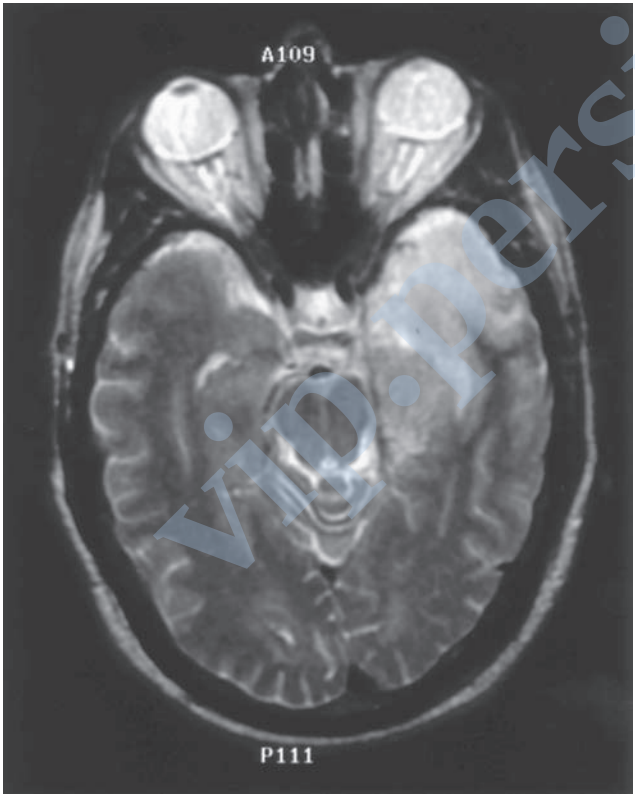

FIGURE 43.1 T2-weighted MRI shows classic high signal intensity lesion in left temporal lobe in herpes encephalitis.

areas of hemorrhagic necrosis, the CSF may contain RBC or xanthochromia. RBC in the CSF may inhibit the PCR, giving a false-negative result.

A. Therapeutic approach.

1. **Antiviral activity.** Acyclovir is the antiviral drug of choice for HSV-1 encephalitis. It is given at a dosage of 10 mg per kg every 8 hours (30 mg per kg a day) IV, each infusion lasting >1 hour, for a period of 3 weeks. IV acyclovir can cause transient renal insufficiency secondary to crystallization of the drug in renal epithelial cells. For this reason, it is recommended that acyclovir be infused slowly over a period of 1 hour and that attention be paid to adequate IV hydration of the patient.
2. **Anticonvulsant therapy.** Seizure activity, either focal or focal with secondary generalization, occurs in two-thirds of patients with HSV-1 encephalitis. Anticonvulsant therapy is indicated if seizure activity develops, and the following drugs are recommended.
   a. **Lorazepam** at dosages of 0.1 mg/kg for adults and 0.05 mg/kg for children, or diazepam at 5 to 10 mg for adults and 0.2 to 0.3 mg/kg/dose for children.
   b. **Phenytoin** at a dosage of 18 to 20 mg per kg at a rate no faster than 50 mg per minute, or fosphenytoin at a dose of 18 to 20 mg PE per kg no faster than 150 mg per minute. The daily maintenance dosage of phenytoin should be determined by serum levels.
3. **Therapy for increased ICP.** Increased ICP is a common complication of herpes encephalitis and is associated with a poor outcome. Increased ICP should be aggressively managed as outlined in **I.A.3.**

B. Expected outcome. Among untreated patients with HSV-1 encephalitis, the mortality is higher than 70%, and only 2.5% of patients return to normal function after recovery. Patients treated with acyclovir have a significantly lower mortality of 19%, and 38% of these patients return to normal function.

C. Referrals. Because the clinical diagnosis of herpes encephalitis typically requires interpretation of the neurologic presentation, the EEG, neuroimaging studies, and CSF, the diagnosis of this severe and devastating neurologic illness should be made in consultation with a neurologist.

III. HERPES ZOSTER (SHINGLES)

A. Therapeutic approach. Oral valacyclovir 1,000 mg three times a day has been found superior to acyclovir in reducing zoster-associated pain. Oral acyclovir 800 mg five times a day and valacyclovir accelerate the rate of cutaneous healing and reduce the severity of acute neuritis and are most beneficial if treatment is initiated within 48 hours. Neither valacyclovir nor acyclovir reduces the incidence or severity of postherpetic neuralgia. For immunosuppressed patients, and for those with zoster ophthalmicus, many experts recommend the use of IV acyclovir. Ganciclovir can be considered an alternative agent for treatment. Corticosteroids have been proposed as adjunctive therapy in immunocompetent patients with varicella-zoster virus encephalitis.

B. Side effects. Oral acyclovir therapy has not been associated with renal dysfunction, but IV acyclovir can cause renal insufficiency. The risk of this complication is decreased by a slow rate of infusion.

C. Prevention. A varicella-zoster vaccine is available to decrease the risk of herpes zoster. Individuals with primary or acquired immunosuppression should not receive the vaccine.

IV. LYME'S DISEASE

Lyme's disease is caused by the spirochete *Borrelia burgdorferi*, which is transmitted by the bite of an infected tick. It is endemic in the coastal northeast from Massachusetts to Maryland (particularly in New York), in the upper midwest in Minnesota and Wisconsin, and on the Pacific coast in California and southern Oregon.

In the majority of patients, initial infection is manifested by the appearance of an annular erythematous cutaneous lesion with central clearing of at least 5 cm in diameter,

called erythema migrans. This lesion appears within 3 days to 1 month after a tick bite. Early disseminated Lyme's disease is characterized by cardiac conduction abnormalities, arthritis, myalgia, fatigue, fever, meningitis, and cranial and peripheral neuropathy and radiculopathy. The most common neurologic abnormality during early disseminated Lyme's disease is meningitis. The clinical features are typical of viral meningitis with symptoms of headache, mild neck stiffness, nausea, vomiting, low-grade fever, and photophobia. These symptoms may be associated with unilateral or bilateral facial nerve palsy or with symptoms of radiculitis (paresthesia and hyperesthesia) with or without focal weakness, transverse myelitis, mononeuritis multiplex or cognitive difficulties.

The majority of patients with Lyme's disease have or have had an erythema migrans lesion. The diagnosis of Lyme's disease begins with a serologic test for antibodies against *B. burgdorferi*. Most laboratories use an enzyme-linked immunosorbent assay technique. False-positive serologic results are a problem with this test for two reasons:

1. Tests can be performed on identical sera in different laboratories with different results. Because these tests are not well standardized, it is important to use a laboratory that is reliable in performing this test. A positive test result may indicate only exposure to *B. burgdorferi* rather than active infection. Persons who live in high risk areas may have measurable antibodies without having Lyme's disease.
2. False-positive serologic results can occur with rheumatoid arthritis, Rocky Mountain spotted fever, infectious mononucleosis, syphilis, tuberculous meningitis, and leptospirosis.

When the ELISA is positive, then a Western blot should be obtained. The CSF is generally abnormal in neurologic Lyme's disease. The typical spinal fluid abnormalities include lymphocytic pleocytosis (100 to 200 cells per mm^3), an elevated protein concentration, and a normal glucose concentration. The CSF should be examined for intrathecal production of anti-*B. burgdorferi* antibodies, and an antibody index should be calculated. The antibody index is determined as the ratio of (anti-*Borrelia* IgG in CSF/anti-*Borrelia* IgG in serum) to (total IgG in CSF/total IgG in serum) and is defined as positive when the result is ≥ 2. The use of the antibody index to determine that there is an intrathecal production of antibodies is important as antibodies can be passively transferred from serum to CSF giving a false positive result, and Lyme's antibodies may persist in CSF for years.

A. Therapeutic approach.

1. Patients with facial nerve palsy without other neurologic manifestations can be treated with doxycycline 100 mg by mouth twice a day for 14 to 28 days. *Doxycycline should not be given to pregnant women.*
2. Parenteral ceftriaxone is recommended for patients with neurologic complications of Lyme's disease, although oral doxycycline may be equally effective in the absence of brain or spinal cord involvement. The adult dosage of ceftriaxone is 2 g per day, which may be given in a single daily dose, and the dosage for children is 75 to 100 mg per kg a day (up to 2 g per day). Treatment is given for at least 2 weeks and should be continued for an additional 2 weeks if the response to treatment is slow or there is severe infection.
3. Alternatives to ceftriaxone are penicillin G and cefotaxime. Penicillin G is administered at an adult dosage of 3 to 4 million units (miU) every 4 hours for 10 to 14 days or at a child dosage of 250,000 U per kg a day in divided doses. The major side effect of penicillin G is hypersensitivity reaction. Cefotaxime is given at dosages of 2 g three times a day for adults and 150 to 200 mg per kg a day (every 6 hours) for children.

B. Expected outcome. The condition of patients with neurologic complications of early disseminated Lyme's disease (meningitis, cranial neuropathy, and peripheral neuropathy) should improve clinically within days, although improvement of facial weakness and radicular symptoms can take weeks. Prolonged antimicrobial therapy does not improve symptoms of post-Lyme's syndrome and is not recommended.

C. Prevention. The deer tick is the usual vector of Lyme's disease in the northeastern and the midwestern United States. Wearing protective clothing can help decrease the risk of infection. Transmission of infection is unlikely if the tick has been attached for <24 hours.

V. CRYPTOCOCCAL MENINGITIS

The diagnosis of cryptococcal meningitis is made when examination of the CSF shows lymphocytic pleocytosis, a decreased glucose concentration, and a positive result of a CSF cryptococcal antigen assay, fungal smear, or culture.

A. Therapeutic approach. The management of cryptococcal meningitis is divided into induction, consolidation and maintenance (suppressive therapy). Induction therapy includes amphotericin B 0.7 to 1 mg per kg a day in combination with flucytosine 100 mg per kg a day divided into four daily doses for at least 4 weeks. Treatment then is switched to consolidation therapy with fluconazole 400 mg per day for a minimum of 8 weeks. Present guidelines recommend slight modifications for induction and consolidation therapy in HIV infected patients and in organ transplant recipients. In the treatment of patients with HIV infection, fluconazole 200 mg per day is continued for lifelong suppressive therapy.

B. Side effects. The most important adverse effect of amphotericin B is renal dysfunction, which occurs in 80% of patients. Renal function, hemoglobin concentration, and electrolytes should be monitored closely. Renal toxicity appears to be reduced or prevented by means of careful attention to serum sodium concentration at the time of administration of amphotericin B. If renal insufficiency develops, AmBisome (Fujisawa, Deerfield, IL, USA) 5 mg per kg a day or amphotericin B lipid complex 5 mg per kg a day can be substituted for amphotericin B. Flucytosine is generally well-tolerated; however, bone marrow suppression with anemia, leukopenia, or thrombocytopenia can develop. These hematologic abnormalities occur more often when serum concentrations of the drug exceed 100 mg per ml; therefore serum concentrations of flucytosine should be monitored and the peak serum concentration kept well below 100 mg per ml.

VI. NEUROSYPHILIS IN IMMUNOCOMPETENT PATIENTS

In immunocompetent patients, the clinical presentation of neurosyphilis falls into one or more of the following categories: (1) asymptomatic neurosyphilis, (2) meningitis, (3) meningovascular syphilis, (4) dementia paralytica, and (5) tabes dorsalis. The diagnosis of neurosyphilis is based on a reactive serum treponemal test and CSF abnormalities. In neurosyphilis, there is often a mild CSF mononuclear pleocytosis with a mild elevation in the CSF protein concentration or a reactive CSF venereal disease research laboratory (VDRL) test. A positive CSF VDRL test establishes the diagnosis of neurosyphilis. A nonreactive CSF VDRL result does not exclude neurosyphilis. The CSF VDRL test is nonreactive in 30% to 57% of patients with neurosyphilis. A nonreactive CSF fluorescent treponemal antibody absorption test (FTA-ABS) excludes the diagnosis of neurosyphilis in all cases except early syphilis. A reactive CSF FTA-ABS is nonspecific and cannot be used to make a diagnosis of neurosyphilis.

A. Therapeutic approach. The regimen recommended by the CDC for management of neurosyphilis is IV aqueous penicillin G at 18 to 24 miU per day (3 to 4 miU every 4 hours) for 10 to 14 days. An alternative regimen is intramuscular procaine penicillin at 2.4 miU per day and oral probenecid at 500 mg four times a day, both for 10 to 14 days.

B. Expected outcome. The serum VDRL titer should decrease after successful therapy for neurosyphilis. The serum fluorescent treponemal antibody absorption test and the microhemagglutination—*Treponema pallidum* test remains reactive for life. The CSF WBC count should be normal 6 months after therapy is completed. If on reexamination of the CSF, the WBC count remains elevated, repetition of treatment is indicated.

VII. TUBERCULOUS MENINGITIS

A. Clinical presentation. Tuberculous meningitis manifests as either subacute or chronic meningitis, as a slowly progressive dementing illness, or as fulminant meningoencephalitis.

The intradermal tuberculin skin test is helpful when the result is positive. Radiographic evidence of pulmonary tuberculosis is found more often in children with tuberculous meningitis than in adults with tuberculous meningitis. The classic abnormalities at CSF examination are decreased glucose concentration, elevated protein concentration, and polymorphonuclear or lymphocytic pleocytosis. The CSF pleocytosis is typically neutrophilic initially but then becomes mononuclear or lymphocytic within several weeks. Acid-fast bacilli are difficult to find in smears of CSF. Culture of CSF is the standard for diagnosis but is insensitive. Cultures are reported to be positive in 25% to 75% of cases of tuberculous meningitis, requiring 3 to 6 weeks for growth to be detectable. PCR assays that detect *Mycobacterium tuberculosis* rRNA in CSF have shown good results in clinical trials.

B. Therapeutic approach. Current recommendations for the management of tuberculous meningitis in children and adults include a combination of isoniazid (5 to 10 mg per kg a day up to 300 mg per day), rifampin (10 to 20 mg per kg a day up to 600 mg per day), and pyrazinamide (25 to 35 mg per kg a day up to 2 g per day). If the clinical response is good, pyrazinamide is discontinued after 8 weeks, and isoniazid and rifampin are continued for an additional 10 months. Ethambutol is added, and the course of treatment is extended to 1 to 2 years for immunocompromised patients. The American Academy of Pediatrics recommends addition of streptomycin at 20 to 40 mg per kg a day to the foregoing regimen for the first 2 months. Pyridoxine may be administered at a dosage of 25 to 50 mg per day to prevent the peripheral neuropathy that can result from use of isoniazid. Corticosteroid therapy is recommended when clinical deterioration occurs after treatment has begun. Dexamethasone can be administered at a dosage of 0.3 to 0.5 mg per kg a day for the 1st week of treatment and followed by oral prednisone.

VIII. NEUROCYSTICERCOSIS

A diagnosis of neurocysticercosis should be considered when a patient has seizures and neuroimaging evidence of cystic brain lesions. Cysticercosis is acquired by ingesting the eggs of the *Taenia solium* tapeworm shed in human feces.

A. Principal forms. The lesions of neurocysticercosis can be found in the brain parenchyma, the ventricles, the subarachnoid space, or in the basilar cisterns (racemose forms). In the parenchymal form, single or multiple cysts are found in the gray matter in the cerebrum and cerebellum. The most common clinical manifestation of parenchymal neurocysticercosis is new-onset seizure activity. In the ventricular form, single or multiple cysts are adherent to the ventricular wall or free in the CSF. Cysts are most common in the area of the fourth ventricle. In subarachnoid neurocysticercosis, cysts are found in the subarachnoid space or fixed under the pia and burrowed into the cortex. In the racemose form, cysts grow, often in clusters, in the basilar cisterns and obstruct the flow of CSF. Hydrocephalus and cysticercotic encephalitis, a severe form of neurocysticercosis due to intense inflammation around cysticerci and cerebral edema, are the most common cause of increased ICP.

B. Diagnosis. The diagnosis of neurocysticercosis depends on clinical features and evidence of cystic lesions demonstrating the scolex at CT or MRI, or other neuroimaging abnormalities (ring enhancing cystic lesions and intraparenchymal calcifications) (Fig. 43.2) suggestive of neurocysticercosis in addition to a positive result of a serologic assay for the detection of antibodies to *T. solium*. Biopsy for histologic demonstration of the parasite is rarely done.

C. Therapeutic approach.

1. **Cysticidal therapy** consists of praziquantel at a dose of 50 mg/kg/day for 15 days, or praziquantel 100 mg/kg in three divided doses at 2-hour intervals (single day course) or albendazole at a dosage of 15 mg/kg a day for 8 days.
2. **Corticosteroids.** Cysticidal therapy frequently causes an inflammatory response with an increase in CSF protein concentration and CSF pleocytosis. This may result in an exacerbation of signs and symptoms. The incidence of an inflammatory response is reduced by the concomitant use of corticosteroids, and their use is recommended both before and during treatment with anticysticidal therapy. Plasma levels of albendazole are increased by dexamethasone; plasma levels of praziquantel are decreased by

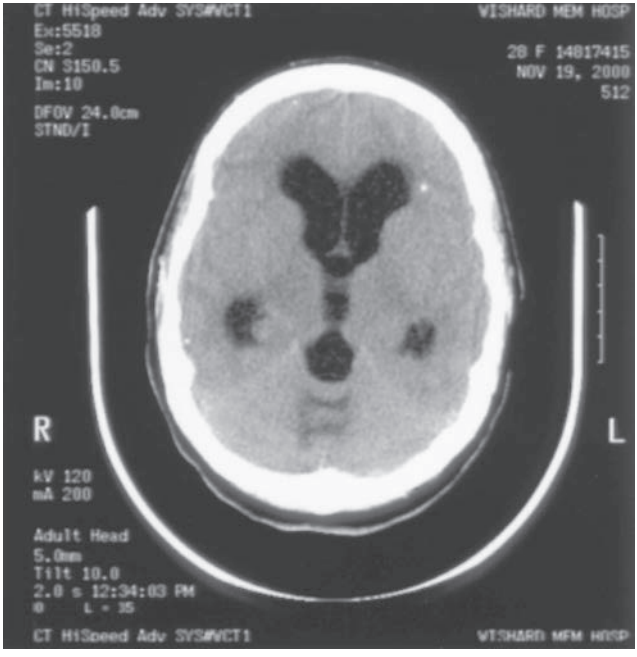

FIGURE 43.2 CT scan shows parenchymal brain calcification and hydrocephalus due to neurocysticercosis.

dexamethasone therapy. This should be taken into consideration when corticosteroid therapy is used to decrease the headaches and vomiting induced by the destruction of parasites in cysticidal therapy. Dexamethasone 24 to 32 mg per day is recommended for patients with subarachnoid cysts, encephalitis, angiitis, or arachnoiditis.

3. **Side effects.** Phenytoin and carbamazepine decrease serum praziquantel levels due to their induction of the cytochrome P-450 liver enzyme system. If one of these anticonvulsants is used with praziquantel, it is recommended that oral cimetidine be added at a dosage of 800 mg twice a day. Cimetidine inhibits the cytochrome P-450 enzyme system, and in this way increases serum levels of praziquantel.
4. **Surgical therapy.** Intraventricular cysts necessitate surgical therapy, and when they obstruct the flow of CSF with resulting hydrocephalus, an intraventricular shunting device is indicated.

D. Expected outcome. The prognosis of patients with parenchymal neurocysticercosis is very good with cysticidal therapy. Cystic lesions should disappear within 3 months of treatment. The mortality is higher among patients with increased ICP, hydrocephalus, or the racemose form of the disease.

E. Prevention. Humans can acquire cysticercosis by eating food handled and contaminated by *T. solium* tapeworm carriers. Persons at high risk of tapeworm infestation who are employed as food handlers should be screened for intestinal parasites. Improved sanitation can decrease the incidence of cysticercosis from contaminated food or drinking water.

Recommended Readings

Brouwer MC, Heckenberg SGB, de Gans J, et al. Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis. *Neurology*. 2010;75:1533–1539.

Cadavid D. Spirochetal infection. In: Roos KL, Tunkel AR, eds. *Handbook of Clinical Neurology. Bacterial Infections of the Central Nervous System*. Edinburgh: Elsevier; 2010:179–219.

Corona T, Lugo M, Medina R, et al. Single day praziquantel therapy for neurocysticercosis. *N Engl J Med*. 1996;334:125.

Del Brutto OH, Wadia NH, Dumas M, et al. Proposal of diagnostic criteria for human cysticercosis and neurocysticercosis. *J Neurol Sci*. 1996;142:1–6.

Halperin JJ, Shapiro ED, Logigian E, et al. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review). *Neurology*. 2007;69:91–102.

Kent SJ, Crowe SM, Yung A, et al. Tuberculous meningitis: a 30-year review. *Clin Infect Dis*. 1993;17:987–994.

Marra CM. Syphilis and human immunodeficiency virus infection. *Semin Neurol*. 1992;12:43–50.

Newton RW. Tuberculous meningitis. *Arch Dis Child*. 1994;70:364–366.

Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:291–322.

Pfister HW, Roos KL. Bacterial meningitis. In: Hacke W, ed. *Neurocritical Care*. Berlin: Springer–Verlag; 1994:377–397.

Roos KL, Tunkel AR, Scheld WM. Acute bacterial meningitis. In: Scheld WM, Whitley RJ, Marra CM, eds. *Infections of the Central Nervous System*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:347–422.

Skoldenberg B. Herpes simplex encephalitis. *Scand J Infect Dis*. 1991;78:40–46.

Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.

Whitley RJ, Gnann JW. Drug therapy: acyclovir—a decade later. *N Engl J Med*. 1992;327:782–789.

Wood MJ, Shukla S, Fiddian AP, et al. Treatment of acute herpes zoster: effect of early (<48 h) versus late (48–72 h) therapy with acyclovir and valacyclovir on prolonged pain. *J Infect Dis*. 1998;178(suppl 1):S81–S84.

CHAPTER

44 Neurologic Complications in AIDS

Bruce A. Cohen

I. GENERAL CONSIDERATIONS

The nervous system is involved early in the course of HIV infection and may produce the presenting clinical manifestations. Early natural history studies found neurologic symptoms and signs in 40% to 70% of patients during the course of the disease, whereas autopsy series demonstrated neuropathologic changes in 90% to 100% of persons with AIDS, affecting all levels of the neuraxis. These neurologic manifestations can result from effects of HIV itself or from opportunistic processes. Acute meningitis, meningoencephalitis, or polyneuritis can mark HIV seroconversion. Subsequently, neuropathy, encephalopathy, myelopathy, and myopathy can occur. Opportunistic illnesses (OI) of the CNS occur in conjunction with marked immune suppression.

Current therapeutic advances with combinations of antiretroviral agents known as highly active or combination antiretroviral therapy (HAART/cART) have had a profound effect on the frequency of both HIV-induced and opportunistic CNS disease. Neurologic complications continue to occur, however; as presentations in persons not known to have HIV infection, and among those who fail cART because of nonadherence or the emergence of resistant HIV strains. Recently, it has become apparent that subtle neurologic manifestations of HIV infection occur in patients on cART, including individuals who appear to be responding to treatment with suppression of systemic disease markers and symptoms. More common conditions causing neurologic complications in AIDS are listed in Table 44.1, although numerous case reports identify a wider spectrum of possible complicating infections.

Some general considerations helpful in approaching HIV+ patients with neurologic disease are listed below:

A. The imaging modality of choice in HIV-related CNS disease is MRI; however, particular imaging patterns may be nonspecific.

B. Multiple pathologic conditions in the CNS may occur concurrently in patients with profound immune suppression.

C. Most OIs appear with significant immune suppression as reflected by CD4+ lymphocyte counts of 200 per mm^3 or less.

D. Neurologic manifestations of OIs in patients with AIDS can be subtle and lack classic disease features seen in other settings.

E. Specific diagnosis of OIs requires confirmation by culture, or demonstration of genetic material in CSF or biopsied tissue. Empiric therapy based on a presumptive diagnosis is appropriate in some circumstances; however, the absence of a typical treatment response should be prompt early further evaluation.

F. HIV-associated cognitive deficits are becoming more subtle in the era of successful cART and may occur in patients who appear to have successful control of systemic disease.

G. Not all neurologic symptoms occurring in HIV+ patients result from HIV or associated opportunistic processes, particularly when the HIV infection appears to be well-controlled. Such patients are subject to all of the common neurologic conditions that affect other populations.

H. Treatment strategies in AIDS are continuously evolving, particularly cART regimens.

II. CONDITIONS ATTRIBUTED TO HIV INFECTION

A. HIV-asssociated neurocognitive disorders (HAND). HIV-associated dementia (HAD; HIV dementia, AIDS dementia complex, and HIV encephalopathy) occurred in

up to 20% of patients in the pre-cART era, usually after marked immune suppression developed, with progressive and disabling impairments in cognition, motor function, and behavior. Since the widespread use of cART, these forms of severe dementia are seen much less frequently. However, subtle forms of measurable cognitive impairment persist and may be increasing in prevalence as a consequence of longer survival and independent evolution of HIV in the relatively sequestered CNS. Three categories have been proposed to describe the current spectrum of HAND (Table 44.2):

1. Asymptomatic neurocognitive impairment (ANI). Individuals with acquired subclinical impairments in at least two cognitive domains on neurocognitive testing, without delirium, symptomatic complaints, or impaired daily activities.
2. Mild neurocognitive disorder. Individuals with clear sensorium and with acquired impairments in at least two cognitive domains causing at least mild interference with daily activities.
3. HAD. Individuals with clear sensorium and with more severe acquired impairments in at least two cognitive domains sufficient to produce marked interference with daily activities.

A recent study employing neurocognitive testing found that 69% of patients with HIV infection taking cART and without detectable virus in the blood or cognitive complaints had subtle cognitive impairments. Of 27% with cognitive complaints, 84% had HAND. Another recent study found HAND in 22% of a large cohort taking cART. Studies have demonstrated discordant presence of HIV in CSF despite absence of virus in blood, and specific HIV viral strains found in CSF, which vary from those found in plasma, and which may have different antiretroviral resistance patterns.

TABLE 44.1 Entities Causing Neurologic Complications in AIDS

Encephalopathy
Diffuse
HIV
PML
CMV
VZV
Syphilis
Toxoplasmosis
Aspergillosis
Toxic (medications)
Metabolic (e.g., hypoxia and sepsis)
Focal
Toxoplasmosis
PML
Lymphoma
Cryptococci
CMV
HSV
VZV
Syphilis
Tuberculosis
Fungal abscess
Nocardia asteroids
Pyogenic abscess
Myelopathy
HIV
CMV
HSV
VZV
Syphilis
Lymphoma
Tuberculosis
Toxoplasmosis
Vitamin B_{12} deficiency
Nocardia asteroides
Pyogenic abscess
Meningitis
HIV
Cryptococci
Syphilis
Tuberculosis
Lymphoma
CMV
HSV
VZV
Other fungi
Neuropathy
HIV
Toxic (e.g., dideoxynucleosides)
CMV
Lymphoma
Syphilis
Vitamin B_{12} deficiency
Myopathy
HIV
Toxic (zidovudine)
Toxoplasmosis
Pyogenic
CMV

Abbreviation: HSV, herpes simplex virus.

TABLE 44.2 Criteria for HAND

A. HIV-associated ANI
Acquired impairment in cognitive functioning involving at least two ability domains
Cognitive impairment does not interfere with daily functioning
Criteria for dementia or delirium are not present
No evidence for an alternative etiology for the ANI
B. HIV-associated MND
Acquired impairment in cognitive functioning involving at least two ability domains
Cognitive impairment produces at least mild interference in function at work, home or in social activities
Criteria for dementia or delirium are not present
No evidence for an alternative etiology for the MND
C. HAD
Acquired impairment in cognitive functioning involving at least two ability domains
Marked interference in function (e.g., inability to work, manage affairs, etc.)
Criteria for delirium not present (clear sensorium)
No evidence of another cause for the dementia

Abbreviation:

MND, mild neurocognitive disorder. Adapted from Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69:1789–1799.

Comorbid conditions may contribute to cognitive impairment in HIV-infected patients including concurrent hepatitis C virus infection, CNS active medications, substance use, and age-related cognitive changes. cART may alter lipid metabolism with accelerated atherosclerosis increasing the risk of cerebrovascular disease with related cognitive deficits.

The pathogenesis of HAD is not well-understood. Pre-cART autopsy studies demonstrated multinucleated giant cells containing HIV, myelin pallor, microglial nodules, and loss of neurons and synaptic density. cART era studies have found less significant correlations between the first three elements and clinical impairments. Neurons are not infected by HIV and die in locations remote from the perivascular macrophages and microglia that harbor the virus. Indirect neurotoxicity resulting from soluble factors released by infected cells causing activation of inflammatory mechanisms and disruption of critical trophic influences which culminate in neuronal apoptosis and neurite damage are pathogenic hypotheses that are currently favored.

1. **Clinical features.** A clinical triad of cognitive impairment, behavioral changes, and motor impairment characteristic of HAD was described early in the AIDS pandemic. Cognitive features include slowness of thought processing, perseveration, impairments of complex attention, and impaired recall of acquired memories. Behavioral features include apathy, withdrawal from social interaction, and depression. Uncommonly, mania or atypical psychoses occur. Motor features include hyper-reflexia, hypertonia, ataxia, and tremors, typically affecting the legs initially but also involving fine motor coordination of the upper extremities. Extrapyramidal features including bradykinesia, facial masking, rigidity, and postural instability may be seen.

   In cART treated patients, these features are attenuated and the temporal course is prolonged. Psychomotor slowing, lassitude, and mild extrapyramidal or fine motor impairments are most commonly seen. The impact can be significant nonetheless, both on the more demanding aspects of daily activities and by altering adherence to cART regimens resulting in loss of viral suppression. Individuals may have mild cognitive abnormalities on testing but no apparent changes in daily functioning. Performance fluctuation on cognitive tests is seen in more mildly affected individuals with some improving and others evolving to more severe impairments.
2. **Diagnosis.** A clear sensorium is a requisite for the diagnosis. Evidence of functional impairment often comes to attention from impaired work performance or reports from a companion who assumes responsibility for handling funds and documents. Withdrawal from social activities is common, and depression may be a comorbid feature. A cognitive screening protocol employing the trailmaking and digit symbol tests has been used with reasonable sensitivity in large clinical trials and can be done quickly

as part of a routine examination. OIs (see the following sections) must be excluded with MRI and CSF analysis, and comorbid metabolic conditions, medications with CNS effects, and influences of recreational drugs or alcohol should be excluded.

MRI in HAND may be normal, demonstrate atrophic changes, or reveal a confluent symmetric leukoencephalopathy. CSF is normal or shows mild-to-moderate protein elevation. In the cART era, many patients with asymptomatic or mild impairments are not severely immune suppressed. Neurocognitive measures are sensitive but must be compared with appropriate normative populations with similar age, educational level, ethnicity, and gender. Depression can be evaluated with instruments such as the Beck depression screening test.

3. **Therapy.**
   a. **Antiviral agents.** Zidovudine, in high doses, which inhibits HIV reverse transcriptase and penetrates into CSF reasonably well, was the first antiretroviral agent shown in a controlled prospective trial to have efficacy in HAD, as measured by serial cognitive testing. Currently, cART therapy with combinations of anti-nucleosides, non-nucleoside reverse transtriptase inhibitors, protease inhibiting agents, and integrase inhibitors has been associated with a marked reduction in the frequency of HAD. Optimal suppression of HIV viral load should be sought as measured by highly sensitive plasma assays. CSF viral load should also be assessed including individuals with HAND despite undetectable HIV in plasma.

   There is no established optimal cART regimen for HAND; however, antiretroviral resistance testing of recovered virus from blood and CSF can aid in the selection of a cART regimen. Although conflicting reports exist regarding the value of selecting agents with higher CSF penetration, such as stavudine, zidovudine, abacavir, efavirenz, nevirapine, and indinavir for combination regimens, or the use of CSF HIV viral load suppression as a marker of treatment efficacy, these measures are often employed, particularly in patients with worsening cognition. New strategies targeting mediators of neurotoxicity are being explored and a search for reliable and timely surrogate markers of CNS disease is an area of current active research. Individuals who qualify should be offered the option of such clinical trials when available.

   b. **Supportive therapy.**

   Apathy and withdrawal can be managed with modafenil 200 to 400 mg daily (not an FDA approved indication) or methylphenidate at 5 to 10 mg two or three times a day.

   Depression is usually managed with selective serotonin reuptake inhibitors such as fluoxetine or others. Tricyclic antidepressants such as nortriptyline at initial dosages of 25 mg at bedtime, increasing in 25-mg increments every 1 to 2 weeks (or similar agents at comparable doses) are alternatives; however, anticholinergic effects of these drugs can precipitate delirium.

   Seizures occur with increased frequency in HIV-infected patients. Because of potential interactions with antiretroviral agents, nonenzyme-inducing anticonvulsants, which are not metabolized by the cytorchrome P-450 system, such as leviracetam, lamotrigine, gabapentin, or pregabalin are preferred.

   Supervision. Progression of HIV-associated cognitive change results in loss of ability to manage personal business and financial affairs. Provisions for assistance and ultimately legal transfer of decision-making powers for both financial and health care decisions, and advance health care directives, should be arranged. Assistance in the home may be needed for the provision of meals and facilitation of personal care. Residence in a sheltered facility can be considered when the need for assistance precludes independent living.

4. **Outcome.** cART has reduced the severity and mortality of HAND; however, by prolonging survival of patients with HIV infection, it may also lead to an increase in prevalence of cognitive impairment. The natural history of HAND in the era of successful cART is currently evolving.

B. HIV myelopathy. Neuropathologic evidence of myelopathy has been found at autopsy in up to half of patients with AIDS, although it affects fewer patients clinically. In the cART era, the frequency appears to be decreasing. Vacuolar changes with foamy macrophages are found predominantly in the myelin of the dorsal and lateral columns of the thoracic spinal cord, resembling changes seen in subacute combined degeneration (see Chapter 45).

Signs of active HIV infection such as microglial nodules and infected macrophages are not associated. The specific cause is unknown; however, a deficiency of transmethylation pathways has been hypothesized.

Rarely, an acute self-limited meningomyelitis has been reported as a seroconversion reaction to HIV.

1. **Clinical features.** Insidiously progressive spastic paraparesis and sensory ataxia with neurogenic bladder dysfunction are typical of vacuolar myelopathy.
2. **Diagnosis** is made on the clinical features once other causes of chronic myelopathy have been excluded, particularly vitamin B_{12} (cobalamin) deficiency, syphilis, human T-cell lymphotropic virus type I infection, and indolent OIs. Myelopathy resulting from recreational inhalation of nitrous oxide or toluene can mimic vacuolar myelopathy. MRI of the spinal cord can be normal or reveal atrophy or nonspecific intramedullary T2 signal abnormalities. CSF should be obtained to exclude other conditions.
3. **Therapy.** No specific therapy has been shown to prevent the progression of myelopathy. Although optimizing cART is recommended, no favorable effect on the neurologic deficits has been demonstrated.

   Supportive therapy is beneficial. Spasticity can be managed with baclofen in divided doses up to 80 mg daily, and/or tizanidine which is more sedating and may be limited to evening use starting at 2 to 4 mg. Anticholinergic agents such as oxybutynin at 2.5 to 5.0 mg three or four times a day may relieve urinary frequency, urgency, and incontinence.

   External supports enhance safer mobility in patients with sufficient leg strength. Motorized scooters or wheelchairs can maintain mobility in weaker patients who are otherwise capable of independent activity.
4. **Outcome.** Most patients with HIV myelopathy follow a slowly progressive course that may stabilize for long periods of time. A long survival time with cART has resulted in a need to manage chronic disability with periodic neurologic evaluation to adjust supportive therapy. Abrupt neurologic changes should prompt evaluation for a superimposed opportunistic process.

C. HIV (DSP). DSP may be the most common neurologic disorder associated with HIV infection producing symptoms in up to 50% of those with advanced infecton. Despite a diminished incidence in some cohort studies since the widespread availability of cART, and the reduced use of neurotoxic antiretroviral agents, a strong association with age and the longer survival of HIV-infected patients may result in continued significant morbidity from this condition.

1. **Pathology.** DSP is a dying back axonal neuropathy predominantly affecting distal small unmyelinated fibers with involvement of myelinated fibers in more severe cases. Direct infection of the nerve fibers has not been shown, and the pathogenesis is currently thought to result from toxic cytokines released by activated immune cells.
2. **Clinical features.** The most prominent symptom of DSP is pain, characterized by symmetric burning, stabbing, or shooting discomfort, which can be disabling in severity. Initial symptoms often include paresthesias and numbness, beginning in the feet and gradually ascending, which may involve the distal upper extremities. With involvement of larger fibers, balance is affected. Examination reveals distal impairment of vibration, pin and temperature perception, and absent or diminished ankle reflexes. Sensory ataxia and weakness of small muscles in the feet, such as extensor hallucis, are not uncommon.
3. **Diagnosis.** The diagnosis is clinical and follows exclusion of other causes of small fiber neuropathy, particularly a toxic neuropathy associated with dideoxynucleoside antiretroviral agents (didanosine and stavudine), which is clinically identical, and differentiated by the onset of symptoms within months of initiating these agents. Other causes of neuropathy in this population such as glucose intolerance, vitamin B_{12} deficiency, and hepatitis C infection may mimic or influence the neuropathic features. Electrophysiologic changes may be modest due to the predominantly small fiber involvement; however, reduced distal sensory nerve action potentials and slowing of nerve conduction velocities may be seen. Quantitative sensory testing may be more sensitive.
4. **Therapy.**
   a. There is no established therapy for DSP, and treatment is directed at symptom relief.
   b. Pain relief is important to optimize function and improve quality of life. There are no agents currently approved by the FDA for the treatment of HIV painful neuropathy,

and regimens for treating other neuropathic pain syndromes are employed including anticonvulsants, antidepressants, and nonspecific analgesics including opioids.

c. Antiretroviral therapy has not been convincingly shown to modify the course of the neuropathy; however, higher plasma viral load has been associated with pain severity in some studies and should be addressed.
d. Neurotoxic agents should be discontinued whenever possible, particularly dideoxynucleosides. Toxic neuropathy may persist for 6 to 8 weeks after discontinuation of these agents, and occasionally may temporarily worsen.
e. Any metabolic deficiencies should be corrected.
f. Topical lidocaine or capsaicin formulations may be effective adjuvants.
g. Nonpharmacologic approaches such as acupuncture, transcutaneous electrical nerve stimulation, biofeedback, and relaxation therapies can be tried.

5. **Outcome.** Symptomatic management can be helpful in alleviating discomfort, but reversal of DSP is unlikely. Acute worsening of DSP sometimes occurs when concurrent pathologies are superimposed.

D. Inflammatory demyelinating polyneuropathy (IDP). Acute IDP usually occurs early in the course of HIV infection and may represent a response to seroconversion. The natural history is similar to that of Guillain–Barré's syndrome (GBS) in non-HIV infected persons and is presumed to result from an immune reaction to the virus that also targets peripheral myelin. Chronic IDP also results from immune-mediated demyelination and may be relapsing or progressive.

1. **Clinical features.** Acute IDP manifests as progressive motor weakness, areflexia, and variable sensory and autonomic symptoms that evolve over days, usually beginning in the distal lower extremities and ascending.

Some cases progress to respiratory insufficiency necessitating mechanical ventilatory support. Chronic IDP may follow a progressive or relapsing course over months with similar motor weakness and areflexia but with more prominent sensory impairment.

2. **Diagnosis.** Typical clinical features are suggestive of IDP. Electrophysiologic studies reveal prominent slowing and motor nerve conduction blocks, prolonged or absent F-wave responses, and variable degrees of axonal damage and denervation. CSF shows prominent protein elevation and in contrast to typical GBS, may be associated with moderate lymphocytic pleocytosis.
3. **Therapy.**
   a. Plasma exchange with a total course of 200 to 250 ml per kg divided into five exchanges over a 2-week period with 5% albumin replacement is effective. An alternative therapeutic option is the use of pooled human immune globulin in dosages of 0.4 g/kg daily for 5 days given as an intravenous (IV) infusion at 0.05 to 4.0 ml/kg/hour as tolerated. IgA deficiency should be excluded before initiating immune globulin transfusions. Patients with chronic IDP need maintenance therapy with one treatment every 2 to 4 weeks. Intervals can be gradually extended as response occurs.
   b. Patients with impending respiratory failure (vital capacity <1,000 ml) need elective intubation until adequate respiratory function returns.
   c. Adjunctive therapy is important to prevent complications of immobility and maintain function in anticipation of neuromuscular recovery. Prophylaxis for venous thrombosis should be maintained until patients are ambulatory. Physical therapy should be initiated at the bedside with passive range of motion to prevent contracture formation advancing to more vigorous therapy with improvement in strength. Neuralgic pain can be treated as in DSP (see II.C.). As strength improves, mobilization may require support devices and orthotics.
4. **Outcome.** Acute IDP resolves with recovery in most patients. Chronic IDP has a more variable outcome, and residual neurologic impairment often persists.

E. HIV myopathy. Myopathy may develop in patients with HIV infection as a result of zidovudine toxicity, HIV-related polymyositis, or, rarely, infection with opportunistic pathogens. Zidovudine myopathy usually appears after at least 6 months of treatment and is thought to result from mitochondrial toxicity. The pathogenesis of HIV myopathy is thought to be an autoimmune myositis. Uncommonly, opportunistic myositis due to toxoplasmosis or other agents can occur in immunocompromised patients.

1. **Clinical features.** Symmetric progressive proximal weakness with elevation of serum creatine kinase levels is typical of HIV and zidovudine myopathy. Myalgia is variable.
2. **Diagnosis.** Clinical features are suggestive. Electromyography demonstrates small myopathic motor unit potentials with increased recruitment, fibrillation, and complex discharges. Concurrent neuropathy is not uncommon. Muscle biopsy may reveal scattered muscle fiber degeneration and inflammatory infiltrates of CD8+ T lymphocytes and macrophages. Mitochondrial abnormalities and inclusions such as nemaline rod bodies may be present.
3. **Therapy.** Patients taking myotoxic agents should discontinue them. For worsening patients and those with acute severe myalgia and immune compromise, biopsy should be considered to exclude opportunistic or inflammatory myositis. Corticosteroids may be started for immune myositis at 40 to 60 mg per day and tapered as response allows. An increased risk of opportunistic infections is associated with steroid therapy in more immune suppressed patients.
4. **Outcome.** Most patients respond to either withdrawal of toxic agents or institution of steroid therapy. Lack of response to empiric measures should prompt muscle biopsy.

F. Aseptic meningitis or meningoencephalitis may appear acutely with HIV seroconversion. Typical symptoms of headache, fever, neck stiffness, and occasionally cranial neuropathy and confusion or lethargy are seen. This condition is often self-limited. A chronic subclinical, aseptic meningitis occurs in many patients with HIV infection. Moderate protein elevation, a modest lymphocytic pleocytosis, elevated gamma globulin index, and occasionally oligoclonal bands are seen. The importance of this condition lies primarily in its potential for causing diagnostic confusion during evaluation for possible neurosyphilis or OI.

III. OPPORTUNISTIC ILLNESSES

OI of the nervous system are currently seen less frequently in patients with HIV infection as a result of cART; however, they continue to occur as presenting manifestations of AIDS, and in patients who have poor responses or lack access to current therapeutic regimens. Due to limitations of space, only the most common OIs are reviewed here. More extensive discussions can be found in the references.

A. Cryptococcus. *Cryptococcus neoformans* is the most common opportunistic pathogen causing meningitis in patients with AIDS. In addition to meningitis, it can cause localized cryptococcomas in brain parenchyma. Extra-neurologic cryptococcal infection can be found in lung, bone marrow, liver, urinary tract (prostate), and skin. The fungus is acquired through inhalation and spreads to the CNS hematogenously.

1. **Clinical features.** The most common presentation is meningitis with symptoms of headache, malaise, and fever. Nausea is associated in approximately one-half and meningismus occurs in one-fourth to one-third of HIV-associated cases. Cranial neuropathy is the most common focal impairment. Papilledema and altered mentation may be seen, and elevated intracranial pressure (ICP) is common. Seizures and focal CNS signs may be observed with parenchymal involvement, and cerebral infarctions due to cryptococcal meningitis have been reported.
2. **Diagnosis.** Imaging studies may be normal or show meningeal enhancement in patients with meningitis. Parenchymal cryptococcoma has variable enhancement patterns. Cystic lesions caused by the extension of organisms into Virchow–Robin's spaces are most often seen in the basal ganglia and do not enhance. Lumbar puncture usually yields CSF under increased pressure. CSF pleocytosis is often modest and may be absent in patients with advanced immune suppression. Depressed glucose and elevated protein levels vary. CSF cryptococcal antigen titers are usually positive, and CSF cultures yield cryptococci in patients with meningitis; however, results of both tests may be negative when isolated crypotcoccomas occur. Definitive diagnosis of isolated parenchymal lesions requires biopsy. Serum cryptococcal antigen is highly sensitive and is positive in 99% of cases, but is not specific for meningitis. Blood cultures may reveal the organism.
3. **Therapy.**
   a. Mortality in cryptococcal meningitis most often occurs in the first 2 weeks. Acute therapy with amphotericin B 0.7 to 1.0 mg per kg a day plus flucytosine 100 mg per

day for 2 weeks is recommended for patients with normal renal function. Liposomal amphotericin B at 4 mg/kg/day, or amphotericin B lipid complex at 5 mg/kg/day can be substituted in patients with renal insufficiency. For patients unable to tolerate amphotericin B, high dose fluconazole (800 to 1200 mg per day) has been used with higher doses being more effective. Flucytosine can be used with fluconazole for acute therapy with some increased risk of toxicity. In patients responding to acute treatment, consolidation therapy with fluconazole 400 mg twice a day is given for 8 weeks or until sterile CSF cultures are obtained.

b. **Adjunctive therapy.** Aggressive management of increased ICP is required with serial lumbar punctures and, if necessary, lumbar drains or ventriculoperitoneal shunts. The goal of treatment is to maintain ICP in the normal range. Acetazolamide therapy is not recommended as it has been associated with increased adverse events.

HAART should be initiated but may be associated with an immune reconstitution inflammatory syndrome (IRIS) in up to 30% of cases, which may mimic persistent or recurrent meningitis (see III.J.).

c. **Maintenance therapy.** Successful sterilization of CSF with induction therapy is followed by maintenance therapy with fluconazole at doses of 200 mg per day until successful restoration of immune function with cART.

4. **Outcome.** The acute mortality for cryptococcal meningitis in retrospective series of patients with AIDS ranges from 11% to 45%, with the majority of deaths during the first 2 weeks. The most important prognostic factor is the degree of obtundation at presentation and the presence and response to treatment of increased ICP. Other factors reported to negatively affect prognosis are CSF cryptococcal antigen titers greater than 1:1,024, extra-neurologic cryptococcal infection, and hyponatremia. CSF should be sampled after completion of acute induction therapy. Persistently positive cryptococcal cultures should be managed with continued higher doses of antibiotics. Serum cryptococcal antigen cannot be used to monitor CSF response.

B. CNS toxoplasmosis. *Toxoplasma gondii* is an intracellular parasite acquired by ingestion which typically remains dormant in the absence of immune suppression. CNS toxoplasmosis remains the most common opportunistic encephalitis and cause of CNS mass lesions in patients with AIDS.

1. **Clinical features.** The most common presentation is a subacute multifocal encephalitis beginning with headache and fever followed by progressive focal and diffuse neurologic deficits appearing over days to weeks. Impaired mentation, hemiparesis, and ataxia are commonly seen. Involvement of the basal ganglia can result in movement disorders. Acute presentation with seizures can occur, and rare instances of chronic diffuse encephalitis mimicking dementia and isolated myelitis have been reported.
2. **Diagnosis.** MRI reveals multiple enhancing lesions in most patients; however, isolated mass lesions can occur in up to 14% of patients and nonenhancing infarction-like patterns, meningoencephalitis, and myelitis have been reported. The appearance of the mass lesions is nonspecific, although a signet ring sign has been suggested to be highly suggestive when present. IgG antibodies to *Toxoplasma* organisms are present in the blood in almost all cases; however, IgM antibodies and convalescent increases in IgG titers are not seen, and rare cases of seronegative pathologically proven toxoplasmosis have been described. Specific antibodies to *T. gondii*, and *Toxoplasma* DNA, can be detected in CSF. Definitive diagnosis requires pathologic demonstration of organisms or their DNA. Radionuclide imaging with thallium single photon emission computed tomography (SPECT) may be helpful in differentiating abscesses from primary CNS lymphomas (PCNSL), but does not distinguish TE from other abscesses. Diagnostic brain biopsy is indicated in patients with negative serology for *T. gondii* and single lesions, or for lesions worsening or failing to respond to antibiotic therapy directed at the organism.
3. **Therapy.**
   a. Because of the typically rapid response to therapy, empiric treatment of patients with AIDS and cerebral lesions suggesting TE, and positive serology for *T. gondii* is warranted. A clinical response is expected within 2 weeks. Optimal therapy combines oral sulfadiazine at 1.5 to 2 g every 6 hours and pyrimethamine in an initial dose of 100 to 200 mg followed by 50 mg per day. Folinic acid at 10 to 15 mg per day is

added to counteract myelosuppression from the pyrimethamine. Patients unable to take sulfa can substitute clindamycin at 600 mg every 6 hours with similar efficacy for acute infection, although subsequent relapse rates may be higher. Atovaquone and azithromycin have also been used in the place of sulfa. Severely ill patients unable to take oral medication have been treated with IV clindamycin or trimethoprim-sulfamethoxazole. Corticosteroids should be avoided in patients treated empirically for TE to prevent diagnostic confusion with CNS lymphoma.

b. Successful initial therapy is continued for 6 weeks or until stable regression of all lesions. Maintenance therapy with sulfadiazine at 500 mg four times a day or clindamycin at 300 mg four times a day, combined with pyrimethamine at 50 mg per day and folinic acid 10 mg per day is continued until stable immune restoration is achieved with cART.

4. **Outcome.** Therapeutic monitoring is particularly important for patients treated empirically for CNS toxoplasmosis. Imaging should be repeated 2 to 3 weeks after the initiation of antibiotic therapy. Failure of lesions to respond should prompt brain biopsy. Biopsy should be considered for any lesion that enlarges despite therapy to exclude an alternate or concurrent process.

C. **CNS lymphoma:** PCNSL has become less frequent with the widespread use of cART. Almost all are B cell lymphomas containing Epstein–Barr's virus (EBV) DNA. Patients with AIDS may also have leptomeningeal lymphoma, usually due to seeding from a cerebral tumor or to metastasis of a systemic lymphoma.

1. **Clinical features.** Symptoms usually evolve over weeks, and diagnosis may be delayed by empiric therapy for presumed toxoplasmosis. Subacutely progressive headache, lethargy, cognitive impairment, and focal neurologic deficits related to tumor location, such as hemiparesis, aphasia, ataxia, or visual field deficits, are common manifestations. Seizures may cause acute presentations. Meningitis, meningoencephalitis, or meningoradiculitis with cranial nerve abnormalities are commonly seen in patients with leptomeningeal lymphoma.
2. **Diagnosis.** PCNSL is usually, but not invariably, contrast enhancing. Single or multiple lesions with diffuse or ring enhancement may be seen. Lesions may be difficult to differentiate from CNS toxoplasmosis or other cerebral abscesses by MRI. SPECT may show increased uptake in PCNSL, in contrast to decreased activity in an abscess, although sensitivity and specificity varies across studies. Brain biopsy is usually required for the diagnosis of PCNSL. MRI may be normal or reveal meningeal enhancement with leptomeningeal lymphoma and diagnosis is usually made on CSF cytologic analysis. Detection of EBV DNA in CSF suggests lymphoma that is confirmed by malignant cells.
3. **Therapy.** Effective cART has had a favorable influence on survival in PCNSL patients and should be aggressively pursued. Cranial irradiation is independently associated with prolonged survival. Limited data are available on chemotherapy which is poorly tolerated in immune suppressed patients. Regimens with antiviral effects directed at EBV might plausibly offer benefit but are yet to be shown effective.
4. **Outcome.** Prognosis of CNS lymphoma in AIDS remains poor with mean survivals measured in months; however, effective cART has had some benefit on prognosis and longer survivals are occasionally seen.

D. **Progressive multifocal leukoencephalopathy (PML).** Prior to the cART era, PML was estimated to affect 4% of AIDS patients and was a presenting illness in up to 20% of these. The incidence has since declined although not to the extent of other OIs. PML results from reactivation of a polyoma virus, JC virus (JCV). The majority of adults have antibodies to JCV indicating prior exposure to the virus and latency. In the setting of immune suppression, possibly linked to the loss of specific CD8+ cytotoxic T-lymphocytes, symptoms of PML may appear.

1. **Clinical features.** Subacute cognitive impairment, visual field defects, hemiparesis, ataxia, and speech or language disturbances evolving over weeks are typical presentations. Some patients come to medical attention with seizures or acute stroke-like presentations while others may evolve over several months.
2. **Diagnosis.** MRI typically demonstrates asymmetric lesions in cerebral white matter on T2-weighted sequences. A scalloped appearance reflecting involvement of the subcortical arcuate fibers is suggestive when present. Frontal, parietal, temporal, basal ganglia,

cerebellar and brainstem lesions may be seen. In contrast to other settings in which the disease occurs, PML lesions in AIDS enhance following contrast infusion in a minority of cases, usually in relatively less immune suppressed patients. Single lesions are sometimes seen. Definitive diagnosis requires confirmation of JCV infection, either in CNS tissue obtained at biopsy, or by demonstration of JCV DNA in CSF in a patient with compatible clinical and imaging features. High-sensitivity JCV polymerase chain reaction (PCR) assays which can detect 50 copies per ml or less should be used to analyze CSF.

3. **Therapy.** Currently, only effective cART has been shown to benefit AIDS-associated PML. CNS IRIS is a potential complication following effective cART therapy and may be difficult to distinguish from worsening PML (see discussion of IRIS in III.J.). Controlled trials with cytosine arabinoside and cidofovir have failed to show additional benefit in HIV-infected cohorts. Case reports suggest possible benefit with mirtazapine but no controlled study has been done. A recent trial of mefloquine was discontinued following an interim analysis.
4. **Outcome.** In the pre-cART era, median survivals were about 6 months, although some patients with less severe immune suppression survived longer. Effective cART therapy has extended survival to years, usually with residual neurologic impairments. Higher JCV load in CSF may be associated with poorer prognosis. Return of specific JCV cytotoxic CD8+ immune cells has been associated with better prognosis. IRIS may occur with institution of cART.

E. Cytomegalovirus (CMV). CMV is ubiquitously acquired, and serologic evidence of exposure is present in most adults. Although a transient systemic illness may occur on acquisition, normal immune function prevents further manifestations. The most common symptomatic CMV infections in patients with AIDS occur in the retina and gastrointestinal tract.

1. **Clinical features.**
   a. CMV encephalitis (CMVE) is characterized by subacute confusion, delirium, impaired attention, memory, and cognitive processing with varying focal signs, including cranial neuropathy, nystagmus, weakness, spasticity, and ataxia. Clinical symptoms evolve over weeks in severely immune suppressed patients. Focal encephalitis with mass lesions or aseptic meningitis can also occur.
   b. CMV polyradiculomyelitis (CMVRM) presents as a subacute motor weakness with areflexia and sphincter dysfunction (usually urinary retention) evolving over days to weeks (see Chapter 46). Painful paresthesias in the perineum and lower-extremities, and features of myelopathy such as a sensory level and Babinski's signs, may be found on examination. Symptoms in the lower extremities may ascend resembling GBS.
   c. CMV multifocal neuropathy is characterized by motor weakness, depressed reflexes, and sensory deficits involving nerves of both upper and lower extremities in an asymmetric pattern evolving over weeks to months. Motor features overshadow the sensory findings.
   d. Less commonly, CMV can cause meningomyelitis or myositis.
2. **Diagnosis.** The clinical syndromes are suggestive, but are not pathognomonic for CMV OI in severely immune suppressed AIDS patients. MRI with gadolinium contrast may reveal enhancement of ventricular ependyma with CMVE, of meninges in some patients with meningoencephalitis or meningomyelitis, and of lumbar nerve roots and conus medullaris in some patients with CMVRM. Normal findings or nonspecific atrophic changes may also be seen. CSF studies in CMVRM characteristically reveal a mixed pleocytosis with a prominent polymorphonuclear component, hypoglycorrhachia, elevated protein. In CMVE, pleocytosis is less common. CSF is normal or reveals nonspecific protein elevation in patients with CMV multifocal mononeuropathy.

   Demonstration of CMV DNA in CSF using PCR amplification techniques is both a sensitive and a specific indicator of active CMV infection. Patients with AIDS and CMV infection of the nervous system typically have systemic infection as well.
3. **Therapy.** No controlled treatment studies of opportunistic CMV infections of the nervous system have been carried out. Three virustatic agents are available for the management of active CMV infection in AIDS, and some authors recommend combination therapy for the treatment of patients with CNS CMV disease, although this may be associated with more toxicity.

a. Ganciclovir is given in an induction dosage of 5 mg per kg IV twice a day for 14 to 21 days followed by a maintenance dosage of 5 mg per kg a day.
b. Foscarnet has better CSF penetration than does ganciclovir. An induction dosage of 90 mg per kg IV twice a day for patients with normal renal function is given for 14 to 21 days and followed by reduction to a maintenance dosage of 90 to 120 mg per day. Doses must be reduced for patients with renal insufficiency.
c. Cidofovir in the setting of normal renal function is given as an IV infusion at 5 mg per kg in 1 L of fluid once a week for 2 successive weeks and then every 2 weeks. The dose must be decreased for impaired renal function, and additional hydration with a second liter of fluid is recommended if tolerable. Probenecid 2 g orally is given 3 hours before the infusion and then 1 g is given 2 and 8 hours after completion of the infusion. Ocular monitoring for hypotony and renal function monitoring are required.
d. Viral resistance may develop to any of these agents during prolonged therapy, and CMV neurologic disease emerging during maintenance therapy for CMV retinitis or enteritis should be managed with induction dosages of alternate agents. Even when drugs have failed individually, patients may respond to combined therapy.

4. **Outcome.** No prospective studies are available to guide therapy for CMV neurologic disease in AIDS. Responses to therapy for CMVE, CMVRM, and multifocal neuropathy are reported anecdotally. Immune suppressed patients should continue maintenance therapy, although the optimal regimen is unknown. CSF studies may be the best markers of neurologic disease activity and should be performed on the completion of induction therapy and for neurologic worsening.

F. Varicella–zoster virus (VZV). VZV commonly occurs in patients with HIV infection at multiple stages of the disease and may produce encephalitis, myelitis, and mono or polyradiculitis. The virus, which causes chickenpox, is acquired early in life and resides latently in sensory ganglia, where it can intermittently produce recurrent radiculitis. Retrograde extension to the CNS along contiguous sensory roots and fiber tracts has been shown to occur. Patients with radiculitis often have self-limited dermatologic eruptions, which may be accompanied by prolonged neuralgia. CNS extension may be marked by vasculitis resulting in cerebral infarction, particularly after ophthalmic zoster, and can result in necrotizing myelitis and brainstem, focal or diffuse cerebral encephalitis.

1. **Clinical features.**
a. VZV radiculitis is characterized by painful paresthesias in a restricted dermatomal distribution of a spinal or trigeminal nerve root. A vesicular rash usually follows, but VZV can occur without the rash. The skin eruption typically heals over weeks; however, pain may persist.
b. VZV myelitis may be limited or progressive resulting in spastic weakness, sensory impairment, and sphincter dysfunction. Myoclonus is sometimes associated as is meningitis. Dermatomal VZV may or may not be associated.
c. Meningitis with lymphocytic pleocytosis, increased protein level, and depressed or normal glucose level may also be seen.
d. Polyradiculitis, which is clinically indistinguishable from CMVRM, can be caused by VZV.
e. VZV encephalitis can be focal or diffuse in patients with AIDS, manifesting as seizures, confusion, progressive language and cognitive impairment, and sensory or motor abnormalities. Progression can be gradual and the level of immune suppression more modest than with other OIs. Meningitis may be associated.
f. VZV vasculitis can cause acute focal features resulting from cerebral or spinal infarction, or diffuse leukoencephalitis due to small vessel involvement.

2. **Diagnosis.** When the characteristic dermatologic eruption occurs, diagnosis of radiculitis is not difficult. In patients with CNS disease, MRI may reveal focal or diffuse areas of high-signal intensity on T2-weighted images of brain or spinal cord. Enhancing focal lesions and meningeal enhancement may be seen. Confirmed diagnosis is based on the demonstration of viral DNA in CSF or tissue or an elevated specific VZV antibody index in CSF.
3. **Therapy.** Patients with HIV infection and VZV radiculitis should be treated with valacyclovir or famciclovir for 7 to 10 days. Neuralgia can be managed with pregabalin

75 to 150 mg twice a day, or gabapentin 300 to 600 mg three or four times a day. Amitriptyline 25 mg at bedtime may be added and increased by 25 mg per day at weekly intervals to 100 mg at bedtime. Some patients may benefit from topical application of capsaicin to the involved cutaneous area three or four times a day. Patients with VZV encephalitis or myelitis should be treated with IV acyclovir for 14 to 21 days at 10 to 12 mg per kg three times a day. Resistance of VZV to acyclovir has been reported, and refractory VZV CNS disease should be managed with foscarnet 60 to 90 mg IV twice a day for 10 to 21 days.

4. **Outcome.** Most patients with VZV radiculitis achieve resolution of the acute symptoms, although recurrences are common in immune suppressed individuals and may involve different dermatomes. The prognosis for progressive myelitis and encephalitis varies; however, limited anecdotal data suggest some patients respond to antiviral therapy.

G. Tuberculosis. *Mycobacterium tuberculosis* (MTB) causes tuberculous meningitis and cerebral mass lesions in HIV-infected patients. Tuberculous meningitis is more common and may evolve subacutely or chronically, often preceded by prodromal signs of systemic illness. Mass lesions include tuberculomas and cerebral abscesses that may evolve more acutely. It has been suggested that cerebral mass lesions are more frequent in HIV associated CNS tuberculosis. The pattern of pathology is influenced by the degree of immune suppression with less granuloma formation in those with lower CD4+ cells counts. Neurologic involvement is more common with immune suppression. In the United States, increased risk is associated with IV drug use, migration from countries with high MTB prevalence, and among individuals who live and work in close contact settings.

1. **Clinical features.** In patients with AIDS and MTB infection, the most common neurologic presentation is meningitis or meningoencephalitis marked by headaches, fever, myalgia, confusion, lethargy, cranial neuropathy, ataxia, seizures, or hemiparesis evolving over weeks. Contiguous extension of basal meningitis to blood vessels of the circle of Willis can result in vasculitis and cerebral infarction. Cerebral abscess formation results in focal symptoms, seizures, headaches, and signs of increased ICP. Tuberculous meningitis can also cause meningoradiculitis, myelitis, anterior spinal artery infarction, and epidural or intramedullary abscess formation. Tuberculous spondylitis can result in vertebral collapse with fever, back pain, and radiculopathy or compressive myelopathy.
2. **Diagnosis.** MRI may reveal focal abscesses in the brain that are indistinguishable from lesions of toxoplasmosis or CNS lymphoma. In MTB meningitis, areas of attenuation typical of infarction, meningeal thickening and enhancement, exudate in basilar cisterns, and hydrocephalus may be seen. CSF is often under increased pressure and reveals a mixed or predominantly lymphocytic pleocytosis, depressed glucose, and prominently elevated protein levels; however, benign CSF indices have been reported in some cases. Smears for acid-fast bacteria are uncommonly positive, although the yield improves somewhat with multiple specimens. CSF cultures may be negative in one-third of cases. Detection of MTB DNA by PCR and MTB antigen assays provide more rapid detection in CSF. Diagnosis of large tuberculous abscesses may require biopsy. Spinal MRI may reveal abscess formation and vertebral collapse in patients with meningitis or myelitis.
3. **Therapy.** Combinations of isoniazid 300 mg by mouth, rifampin 600 mg by mouth, ethambutol at 15 to 25 mg per kg a day by mouth and pyrazinamide at 15 to 25 mg per kg by mouth daily are recommended for the first 2 months, followed by INH and rifampin for the next 10 to 12 months in responders. Pyridoxine (50 mg per day) is added for patients taking isoniazid. Resistance of MTB to these agents is now observed more commonly, and isolates should be tested for sensitivity to the antibiotics employed. Resistance or lack of response to treatment should prompt infectious disease consultation to modify therapy. In patients with tuberculous meningitis, corticosteroids 0.3 to 0.4 mg/kg/day dexamethasone or 1 mg/kg/day prednisone are added for the first 3 weeks and then tapered over the next 3 to 5 weeks. IRIS is not uncommonly seen with reversal of immune suppression following cART (see III.J.).
4. **Outcome.** The mortality of AIDS-associated tuberculous meningitis has been reported to be as high as 33% and to be related to the degree of immune suppression.

Patients with MTB meningitis need follow-up CSF studies 1 to 2 months after initiation of treatment and at completion of primary therapy to detect persistent infection from resistant organisms. Tuberculomas can be followed with serial imaging studies in the absence of life-threatening mass effects. Lesions that enlarge despite therapy should be reevaluated and considered for biopsy to detect resistant organisms or concurrent opportunistic processes.

H. Neurosyphilis. Although not strictly an opportunistic pathogen, overlapping risk factors and a potentially more aggressive course make *Treponema pallidum* infection a particular concern in patients with HIV infection. Increased frequency of CNS involvement and occasional failure of conventional therapy with emergence or recurrence of neurosyphilis despite standard courses of penicillin have been reported.

1. **Clinical features.** Meningitis, meningoradiculitis, meningovasculitis with infarctions of small vessels, meningomyelitis, and encephalitis can occur in patients with AIDS. Cranial neuropathy, headache, and fever may mark syphilitic meningitis, and polyradiculitis may result in a cauda equina syndrome similar to CMVRM. Luetic encephalitis and myelitis can be gradually or subacutely progressive. Mass lesions resulting from gumma formation may manifest with seizures, focal signs, and increased ICP.
2. **Diagnosis.** Aseptic meningitis with mononuclear pleocytosis and elevated protein associated with a positive venereal disease research laboratory (VDRL) test is considered diagnostic of neurosyphilis. A negative VDRL is not exclusionary of the diagnosis. Specific treponemal antibody assays in CSF, such as the direct fluorescent antibody—*Treponemal Pallidum* test and or the fluorescent treponemal antibody absorption test are more sensitive but less specific for neurosyphilis; however, they are exclusionary of neurosyphilis when negative in the CSF. Imaging studies may reveal infarctions in meningovascular syphilis, or masses in patients with gummas. Mass lesions are usually diagnosed at biopsy.
3. **Therapy.** Neurosyphilis should be treated with IV aqueous penicillin G at a dosage of 3 to 4 million units every 4 hours for 14 days. Procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg orally four times a day for 14 days can alternatively be used in patients who are not allergic to sulfa. Some infectious disease specialists add 2.4 million units of intramuscular penicillin weekly for 3 weeks following the IV course. No other therapy has proven efficacy, and penicillin desensitization followed by one of the above regimens is preferred in patients with a history of penicillin allergy if possible. Ceftriaxone 2 g per day IV for 14 days may be an alternative treatment for patients severely allergic to penicillin who do not have cross-sensitivity to cephalosporins.
4. **Outcome.** Although the initial response is good, risk of recurrent neurosyphilis is increased in the setting of HIV infection. Patients with syphilitic meningitis should have CSF studies 3 months following the completion of treatment and at 6-month intervals until the CSF leukocyte count normalizes and the VDRL becomes non-reactive. Subsequent neurologic symptoms should prompt evaluation for recurrence.

I. Other opportunistic infections. Numerous other OIs have been described in HIV infected patients, and a fuller compilation is beyond the scope of this chapter. More extensive reviews are contained in the references below.

J. Immune reconstitution inflammatory syndrome. A potential consequence of the potency of current cART regimens is a rapid restoration of immune responsiveness, which may lead to clinical worsening during treatment, despite improving HIV disease markers, as a result of damage caused by an aggressive immune-mediated response. This is called IRIS and is most commonly seen with treatment of opportunistic infections in conjunction with institution or modification of cART. Some cases occur in the absence of OIs and are presumed to be an inflammatory response to HIV related antigens.

In some cases, a resident OI may be unmasked by the institution of cART and the vigorous immune response which follows, whereas in other instances, an initial improvement in an OI may be followed by clinical worsening, which may cause difficulties distinguishing between treatment failure of the OI and IRIS. Neurologic IRIS has been described with cryptococcus, toxoplasmosis, PML, CNS tuberculosis, CMV, VZV, EBV, and as a progressive encephalitis following initiation of cART when no OI is demonstrated.

Individuals naïve to cART, with low CD4+ counts and high HIV viral loads who experience rapid improvements in these measures appear to be most at risk. Onset usually occurs within 8 weeks of starting cART; however, some cases with longer intervals are reported. IRIS may occur without apparent symptoms detected by inflammatory activity on MRI, and may resolve spontaneously, or cause neurologic symptoms of such severity as to result in mortality. Pathologic reports of CNS IRIS have most commonly identified CD8+ lymphocyte infiltration from perivascular spaces with activated macrophages. MRI may show enlarged enhancing lesions with edema and mass effects suggestive of an inflammatory response in patients with CNS parenchymal disease.

1. **Diagnosis.** Diagnosis requires exclusion of recurrent or new concurrent infection or neoplasm to explain the clinical features. In cases where biopsy is pursued, a vigorous CD8+ inflammatory response in the absence of active infections suggests the diagnosis.
2. **Therapy.** There are no controlled studies addressing therapy. Both spontaneous resolution and resolution associated with corticosteroid therapy are reported. Current practice favors high-dose steroids for patients with severe neurologic symptoms and IRIS. Steroids may be required for several weeks or months and should be gradually tapered to prevent rebound inflammation on withdrawal.

Recommended Readings

Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69:1789–1799.

Canestri A, Lescure FX, Jaureguiberry S, et al. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. *Clin Infect Dis*. 2010;50:773–778.

Cysique LA, Vaida F, Letendre S, et al. Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. *Neurology*. 2009;73:342–348.

Garvey L, Winston A, Walsh J, et al. Antiretroviral therapy CNS penetration and HIV-1-associated CNS disease. *Neurology*. 2011;76:693–700.

Gendelman H, Grant I, Everall IP, et al., eds. *The Neurological and Neuropsychological Manifestations of HIV-1 Infection*. 3rd ed. 2011.

Johnson T, Nath A. Neurological complications of immune reconstitution in HIV-infected populations. *Ann N Y Acad Sci*. 2010;1184:106–120.

Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Morb Mortal Wkly Rep. 2009;58(RR-4):1–198.

Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008;65:65–70.

Portegies P, Berger JR, eds. *HIV/AIDS and the Nervous System. Handbook of Clinical Neurology*. Vol 85, 3rd series. Amsterdam: Elsevier; 2007.

CHAPTER

45 Spinal Cord Disorders

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I. DEVELOPMENTAL DISORDERS

Developmental disorders occasionally cause pain or progressive neurologic dysfunction in adults. Others are found incidentally.

A. Chiari's malformations are characterized by descent of the cerebellar tonsils by 5 mm beyond the foramen magnum, with downward displacement of the medulla and kinking of the cervical spinal cord. Hydrocephalus, bony abnormalities of the skull base, and syringomyelia in the cervical cord are frequently found. Chiari I malformations (not associated with meningomyelocele) frequently do not manifest themselves until adulthood. Approximately 80% of patients will have syringomyelia.

1. No treatment is warranted if the patient has no symptoms. Cranial nerve signs, a history of sleep apnea, and radiologic evidence of syringomyelia should be sought. Neurologic and radiologic follow-up evaluation is warranted, especially for children and young adults.
2. If the patient has symptoms, decompressive suboccipital craniectomy and upper cervical laminectomy with or without ventricular shunting are required. However, patients may be stratified to a more or less aggressive surgical approach, based on structural features of the cisterna magna, extent of tonsillar descent, presence of a syrinx, and intraoperative ultrasound findings.
   a. Respiratory depression is the most common postoperative complication necessitating close monitoring.
   b. Approximately 50% of patients benefit, 25% have no change, and 25% deteriorate.

B. Spina bifida occulta is the anomalous development of the posterior neural arch without an extraspinal cyst. The condition is found in 5% of the population. Cutaneous anomalies often overlie the bony defect. Evidence of other lumbosacral anomalies may be found by means of ultrasonography in infants younger than 3 months or by means of MRI in older patients. Dermal sinus tracts can cause recurrent meningitis. Lipomas and dermoids can impinge on the cord or the cauda equina.

1. Dermal sinus tracts are closed to prevent meningitis.
2. Biopsy is indicated for tissue diagnosis of mass lesions.
3. Surgery is indicated for progressive deficits.

C. Tethering of the cord by adhesions, lipomas, or a tight filum terminale is the most common finding associated with spina bifida occulta. The syndrome often manifests itself after growth spurts or minor trauma. Pain can be the predominant presentation in adults, whereas scoliosis is more common in children. Bladder and bowel symptoms are common in both.

1. Surgery is controversial in the care of children who have no symptoms. Arguments for early prophylactic surgery are strong because symptoms stabilize but rarely are relieved after surgery. Patients should undergo electromyography (EMG) and urodynamic evaluations before a final decision is made.
2. Surgical release stabilizes progression without a marked effect on bladder dysfunction. Results are mixed for the relief of pain. In follow-up care, the possibility of retethering of the spinal cord has to be monitored.

D. Diastematomyelia is splitting of the spinal cord by a bony or fibrous septum. The anomaly can become evident during growth spurts or minor trauma. Spina bifida occulta often is present. Pain is prominent in adults but not in children.

1. The septum is removed in children in response to expected progression.

E. Platybasia (upward displacement of the floor of the posterior fossa) and **basilar invagination** (protrusion of the odontoid through the foramen magnum) decrease the diameter

of the foramen magnum. In adults, these conditions manifest as spastic tetraparesis or lower cranial nerve dysfunction.

1. Surgical options include decompressive suboccipital craniectomy with upper cervical laminectomy.
2. Counseling is indicated for the apparent genetic basis of skull-base disorders.

F. Syringomyelia is a congenital pericentral cavity of the cervical spinal cord that may extend into the thoracic cord or upward into the medulla (syringobulbia). Most lesions are between C2 and T9. It most frequently occurs in the setting of Chiari I malformation, but other etiologies include Klippel–Feil's syndrome, tethered spinal cord, postinfectious, postinflammatory, post-traumatic, and spinal neoplasms.

1. Syringomyelia usually manifests itself in adolescence or adulthood. The classic syndrome of upper-extremity weakness and atrophy (often asymmetric) with dissociated sensation in a "cape distribution" is found in 75% of cases. Enlargement of the syrinx can result in Horner's syndrome and myelopathy. Sleep-related respiratory disturbances are not uncommon, especially in syringobulbia.
2. Although this disorder often is slowly progressive, long periods of stabilization, as well as of acute deterioration, can occur. Neck or arm pain often is a prominent problem among older patients. Scoliosis may be prominent in younger patients.
   a. Surgery may not be indicated if symptoms are minimal or very severe, if symptoms have been present longer than 5 years, or if the cord is of normal size on MRI.
   b. Surgery may be indicated in the presence of mild deficits of short duration, enlargement of the cord on MRI, and predominant symptoms of pain or spasticity.
3. Surgery is indicated in progressive cases.
   a. Results of surgery. The condition of approximately one-third of patients improves, of < one-half stabilizes, and of approximately one-fourth deteriorates.
      (1) Pain and paraparesis show the best responses.
      (2) Sensory loss, lower motor neuron signs, and brainstem findings are the symptoms least likely to be relieved.

II. VITAMIN DEFICIENCIES

A. Vitamin B_{12} (cobalamin) deficiency is the most common disorder of the spinal cord for which specific medical therapy exists.

1. **Pernicious anemia** is the most common cause of vitamin B_{12} deficiency and is thought to be an autoimmune disorder affecting all races and both sexes. Antibodies to parietal cells are found in almost 90% of patients, and antibodies to intrinsic factor are found in somewhat more than 60%. Increased clinical suspicion, automated RBC indices, and insidious onset (it takes 5 to 10 years to deplete normal body stores of cobalamin) make the fully developed classic hematologic and neurologic manifestations clinical rarities today.
2. **Other causes** of vitamin B_{12} deficiency include **gastrectomy, diseases of the terminal ileum** (Crohn's disease and diverticulosis), and less severe **gastric atrophy** (causing food-bound malabsorption). Dietary causes, once thought to be uncommon except in vegans and their breast-fed infants, may be an increasing problem among the elderly. **Nitrous oxide exposure** during anesthesia can result in precipitous neurologic manifestations in patients with "silent" deficiencies or marginal body stores. Nitrous oxide can also be the cause of an insidious myelopathy if abused.
3. **Clinical features.**
   a. **Hematologic features.** The classic severe megaloblastic anemia of insidious onset is relatively rare. Approximately 25% of patients have normal hemoglobin values, 25% have normal RBC indices, and 10% to 20% have completely normal CBCs.
   b. **Neurologic features.** Approximately 25% to 50% of patients with vitamin B_{12} deficiency have neurologic symptoms or signs at diagnosis. One study showed that 27% of patients were without neurologic problems but had abnormal signs. Most patients

experience leg dysesthesia as the first symptom. Neurologic presentations include the following:
(1) **Polyneuropathy,** autonomic disturbances, and decreased visual acuity.
(2) **Subacute combined degeneration of the spinal cord** affecting the posterior and lateral columns. T2 hyperintensity in the posterior columns may be apparent on spinal MR.
(3) **Personality changes, dementia,** and psychiatric illness, including psychosis.

4. **Diagnosis.** In large-scale screening of elderly persons without symptoms, between 10% and 20% may have cobalamin deficiency.
   a. **Serum vitamin B_{12}** (cobalamin). The sensitivity, specificity, and accuracy of this commonly used assay are controversial. Patients can have normal levels and cobalamin-responsive neurologic disorders; low levels and nonresponsive deficits; or low levels but no other evidence of deficiency. Despite these severe shortcomings, measurement of cobalamin in the serum is the screening test that is the most widely available. For most patients, serum folate should be measured at the same time. Cobalamin levels in blood are light and temperature sensitive.
   b. The **peripheral blood smear** should be examined for macroovalocytes and hypersegmentation of neutrophils. It may be abnormal in the absence of clinically significant anemia, although the sensitivity is low in mild vitamin B_{12} deficiency.
   c. **Methylmalonic acid (MMA)** (urine and serum) and serum **homocysteine** (HCYS) accumulate in vitamin B_{12} deficiency. HCYS level is also elevated in folate deficiency. Assays for these metabolites can be helpful in selected cases. In comparison with serum cobalamin measurement, these assays are characterized by the following:
      (1) **Advantages** include possibly better sensitivity and specificity.
      (2) **Disadvantages** are expense and limited availability.
         (a) Elevated MMA and HCYS levels are found in hypovolemia, renal failure, and inherited disorders.
         (b) HCYS level is elevated in hypothyroidism, pyridoxine deficiency, and psoriasis.
   d. **Intrinsic factor antibody testing** is specific but suffers from low sensitivity (<60%). However, its low cost and simplicity make this test useful as an alternative confirmation of pernicious anemia.
   e. **Parietal cell antibody testing** is sensitive (>90%) but suffers from low specificity. A negative result makes pernicious anemia unlikely.
5. **Treatment.**
   a. For patients with pernicious anemia, severe deficits, or poor compliance, the usual treatment is cyanocobalamin in the following dosages: 1 mg per day intramuscularly (IM) for 7 to 12 days, then 1 mg per week IM for 3 weeks, and then 1 mg every 1 to 3 months IM for life. Less severe deficiencies can be initially treated with every other day injections for the first week, then weekly injections for the first month. Monthly injection is the standard maintenance regimen and provides the greatest ease of compliance. If longer intervals are used, MMA levels should document adequate treatment and compliance.
   b. The unusual patient with pernicious anemia and a strong aversion to injections may be offered **oral therapy** after initial cobalamin repletion. Large doses are needed, because only 1% to 3% of cobalamin is absorbed independently of intrinsic factor. Monitoring of cobalamin levels is needed until compliance is assured. The usual dosage is 1 to 2 mg per day by mouth for life. Recent evidence suggests oral therapy is at least as efficacious as parenteral therapy in reversing the clinical and biochemical indicators of vitamin B_{12} deficiency.
   c. For patients who are compliant, absorb oral vitamin B_{12} (the results of a standard Schilling test is normal and serum cobalamin level normalizes), have mild deficits, and want to avoid monthly injections, cyanocobalamin can be given at 50 to 1,000 µg per day by mouth for life. Cobalamin or MMA levels or both should document adequacy of the dosing schedule.
6. **Prognosis.** Degree of recovery depends on the severity and duration of deficits at diagnosis. Severe deficits or symptoms that have existed for more than 1 year often respond incompletely. Most improvement occurs within 6 to 12 months. If a patient has not

shown some improvement after 3 months, a response is unlikely. Either the diagnosis was in error or a vitamin B_{12} deficiency was coexistent but not causal (commonly observed in dementia).

7. **Therapeutic strategy.** Predicting which neurologic deficits will respond to vitamin B_{12} is imprecise. Patients with symptoms or signs consistent with vitamin B_{12} deficiency and laboratory evidence of a possible vitamin B_{12} deficiency should be given a 6-to 12-month trial of vitamin B_{12} if other treatable disorders (including folic acid deficiency) have been eliminated.

B. Folic acid deficiency is not generally appreciated as a cause of neurologic dysfunction similar to that found in vitamin B_{12} deficiency. As in vitamin B_{12} deficiency, the neurologic deficits can develop with normal or mildly abnormal hematologic values. The incidence of severe neurologic deficits is lower in folate deficiency than in cobalamin deficiency.

1. **Dietary inadequacy** is the most common cause of folate deficiency, especially among the elderly. Pregnancy, alcoholism, generalized malabsorption, antiepileptic medication, chemotherapy, and congenital defects in absorption or one-carbon enzymes are other potential causes.
2. **Clinical features.**
   a. Instances of dementia, depression, psychosis, polyneuropathy, and subacute combined degeneration of the spinal cord all have been shown to be responsive to folate supplementation. Changes in mental status and higher cortical functions may be the most common presentations in adults.
   b. An association between maternal folate supplementation and prevention of neural tube defects in the offspring has been found. Folate appears to correct a subtle block in one-carbon metabolism rather than replenish a deficiency.
3. **Diagnosis.**
   a. A low-**serum folate** level indicates a negative balance and predicts the likelihood of folate deficiency if uncorrected. The serum level is a poor predictor of total body stores. Because RBC folate level is much greater than serum folate level, hemolyzed specimens should be rejected.
   b. **RBC folate** level indicates body stores during the lifetime of the RBC. The specificity, sensitivity, and usefulness of the value obtained by means of radioassay (the most common technique) are controversial. If both the serum and RBC folate levels are low, ongoing folate deficiency is suggested.
   c. Elevated **serum HCYS** level with a normal serum MMA level is also a marker of folate deficiency and can be helpful in equivocal cases. Because cobalamin deficiency also elevates HCYS level, MMA has to be measured at the same time to differentiate the two deficiencies.
   d. A search for a gastrointestinal disorder should be undertaken when signs of malabsorption exist or if a dietary cause is not clear. Gastroenterologic referral and jejunal biopsy should be considered. Concurrent vitamin B_{12} deficiency can cause folate malabsorption and result in low serum and RBC folate levels. (Vitamin B_{12} deficiency is more likely to elevate serum folate levels consistent with the methylfolate trap hypothesis.)
4. **Treatment** with folic acid at a dosage of 2.5 to 10.0 mg per day by mouth is sufficient in dietary deficiency. Parenteral (IM) doses are given in malabsorption syndromes. Treatment is for life or until body stores are replete and etiologic factors corrected. A multivitamin should also be taken. Compliance and adequacy of treatment can be monitored with HCYS levels.
5. There is uncertainty concerning the possible **epileptogenic properties** of folic acid. Folate deficiency should be confirmed with serum HCYS measurement in the care of patients with seizures. Unless severe hematologic or neurologic deficits are present, less aggressive dosing (1 to 2 mg per day) may be best. Normalization of serum HCYS level is necessary to document compliance and to verify adequate treatment.
6. **Prognosis** is generally good if treatment is started early. Poor responses in cases of dementia or depression with folate deficiency probably represent the concurrence of two common disorders in the elderly.

C. Vitamin E deficiency can cause polyneuropathy, myopathy, scotomata, and demyelination within the posterior columns and spinocerebellar tracts of the spinal cord. The ataxia and posterior column manifestations of abetalipoproteinemia, a rare autosomal recessive disorder of lipoprotein metabolism are responsive to vitamin E supplementation. Rare cases of vitamin E deficiency usually manifest as long-standing malabsorption and steatorrhea. An isolated autosomal recessive defect in transport also exists. Reversal of neurologic deficits with vitamin E supplementation is variable but can be dramatic. Because prognosis appears related to duration of symptoms, a high index of symptoms is warranted. Large oral dosages of vitamin E (800 to 3,600 U per day) or semiweekly injections of α-tocopherol have been used.

D. Copper deficiency can cause a myelopathy marked by a spastic gait and sensory ataxia. An axonal, sensorimotor polyneuropathy frequently coexists. The myelopathy is most pronounced in the cervical cord compared with the thoracic and lumbar segments. It most frequently presents in the fifth and sixth decades and is more common in women. The clinical and radiographic features are often similar to those seen in subacute combined degeneration from B_{12} deficiency. In fact, the two conditions may coexist. Causes of copper deficiency include prior gastric surgery, malabsorption (e.g., in celiac disease), parenteral feeding deficiency, and excessive zinc intake (as can be seen with use of certain denture creams). However, in many cases, the cause remains unclear. Hematologic manifestations of copper deficiency include anemia or neutropenia. Treatment with copper supplementation may prevent further neurologic deterioration, and variably can improve symptoms. Supplementation is typically oral, at 6 mg per day for 1 week, then 4 mg per day for 1 week and 2 mg per day thereafter.

III. VASCULAR MALFORMATIONS OF THE SPINAL CORD

A. Classification. Spinal cord vascular malformations can be classified into intramedullary arteriovenous malformations (AVMs), perimedullary AVMs, spinal-dural arteriovenous fistulas, epidural AVMs, paravertebral vascular malformations, vertebral hemangiomas, and complex angiomatosis. Of these, spinal-dural arteriovenous fistulas are the most common, making up about 70% of all lesions, and thus the rest of this section will focus on this entity.

B. Clinical features. Patients present with a variety of symptoms distal to the malformation, including progressive paraparesis or radiculopathy, sensory impairment, sphincter disturbances, and pain. When hemorrhage occurs within the lesion, it may result in an acute medullary syndrome.

C. Diagnosis. Most fistulas are located in the mid to lower dorsal spinal cord (T6–T12). Enhanced MRI is the screening modality of choice, but a spinal-dural fistula may escape detection even on high quality MRI. Therefore, selective spinal arteriography is usually indicated.

D. Treatment. Endovascular embolization can often cure these lesions. Open surgery is indicated if embolization fails. In some patients, a combination of both embolization and open surgery is the best therapeutic option.

E. Prognosis. Fistulas in the mid to lower thoracic cord respond best to treatment. Motor symptoms tend to improve most (up to two-thirds of patients), followed by pain and sensory disturbances (up to one-third of patients), and finally sphincteric dysfunction, which is seldom reversible.

IV. SPINAL CORD INFARCTION

Although spinal cord infarctions account for only about 1% of all strokes, they are a cause of significant morbidity. Some common etiologies include prolonged episodes of arterial hypotension, surgical procedures, and pathologies affecting the aorta, disk prolapse or herniation, and arteriopathy; however, in some cases, no cause can be identified. Rarely, spinal cord infarction may be a complication of transforaminal cervical epidural steroid injection. In terms of prevention, motor evoked potentials are commonly been used during

aortic surgeries (e.g., during thracoabdominal aortic aneurysm repair) to alert the surgeon to impending spinal cord ischemia, thus reducing the incidence of paraplegia. The neurological symptoms of spinal cord ischemia are referable to the involved artery or segment of the spinal cord. Pain at the level of infarction is also a common finding. Diagnosis is aided by contrast-enhanced MRI. This should include diffusion-weighted imaging as well, as it may take up to 24 hours for ischemic lesions to appear on conventional sequences (Fig. 45.1). Therapeutic interventions include lumbar CSF drainage with or without vasopressor therapy. Treatment is also supportive and focused on the underlying pathology and secondary stroke prevention (patients generally receive an antiplatelet unless there is a contraindication). Unilateral infarcts have a more favorable prognosis; however, prognosis is largely dependent on the severity of the initial deficit. There is some evidence to suggest that intact proprioception at the onset of the deficit also carries a more favorable prognosis.

V. ACUTE SPINAL CORD INJURY

A. Etiology. The major causes of acute spinal cord injury are motor vehicle accidents, falls, recreational injuries, and acts of violence. Fracture and compromise of the spinal cord (or cauda equina) occur most often at cervical and thoracolumbar levels. Although thoracic fractures are less common, neurologic injury is more common because of the narrowness of the spinal canal.

B. Prevention. Proper use of passive and active restraints in automobiles and use of helmets by motorcyclists and bicyclists prevent head and spinal injuries. For example, the Think First program, which addresses educational issues for youth in kindergarten through 12th grade and is actively supported by the neurosurgical community, should be embraced by health care providers.

C. Prognosis. Improvement of even one level can have a dramatic effect on function, especially in cervical cord injuries (Table 45.1). Final neurologic function depends on severity of initial injury, prevention of secondary damage, and successful management of the complications and sequelae of the acute injury and intensive rehabilitation. Neurologic assessment 72 hours after injury according to American Spinal Injury Association guidelines is useful in estimating outcome.

1. Features suggesting a possibility of neurologic improvement are as follows:
   a. Motor or sensory function below neurologic level (incomplete lesion).
   b. Degree to which motor strength is preserved below neurologic level.
   c. Preservation of pinprick response in addition to light touch below neurologic level.
   d. Age < 30 years.
   e. Residual anal sphincter tone.
   f. Relatively well-preserved vertebral alignment.
2. Features suggesting a poor prognosis are as follows:
   a. Absence of residual function (complete lesion).
   b. Hemorrhage or multilevel edema on MRI.

D. Principles of treatment.

1. **Immobilization of the spine** at the scene, in transport, and in the emergency department is critical in preventing further damage.
2. **ABCs of trauma care;** supplemental oxygen should be provided.
3. **Primary survey** of associated damage.
   a. Alteration of sensorium necessitates investigation for accompanying head injury.
   b. Neurologic level may mask the usual symptoms and signs of thoracic, abdominal, pelvic, or extremity injury. More reliance is placed on objective tests.
4. **Radiologic evaluation** of level of skeletal injury.
5. **Skeletal traction** for stabilization and closed reduction if indicated.
6. Assessment of **neurologic level of injury**.
   a. The neurologic level of injury is the most caudal segment at which both motor function and sensory function are intact bilaterally (Table 45.2).
   b. The completeness of the injury is defined by American Spinal Injury Association classes grades A through E, which describe function at least three levels below the

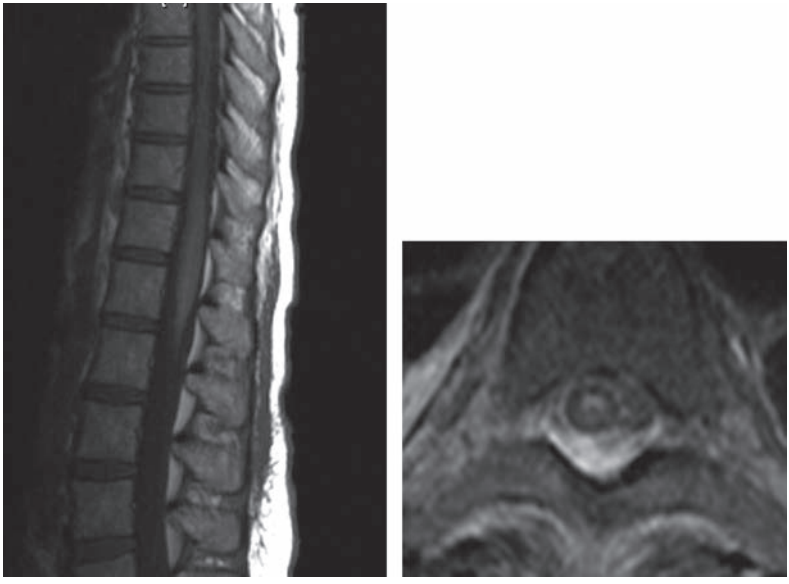

FIGURE 45.1 A 33-year-old woman with systemic lupus erythematosus, antiphospholipid antibody syndrome, status post-quintuple coronary-artery-bypass graft, who developed acute cardiac tamponade and hepato-renal syndrome. She was found to have flaccid paraplegia of the lower extremities. Pre- and post-contrast MRI (sagittal and axial) of the lower thoracic spinal cord and conus medullaris demonstrates abnormal high signal intensity most prominent at the levels of T11 and T12, as seen on the T2-weighted images. These findings are consistent with spinal cord ischemia. (Courtesy of José Biller.)

neurologic level of injury. Grade A indicates a complete level, grade E indicates recovery, and grades B through D describe incomplete levels.

7. **Secondary survey** and stabilization of patient's condition.
8. **Transport** to spinal cord injury center.
9. **Surgical decompression** preferably done within 24 hours in select cases.
10. **Medications** to prevent secondary (oxidative) damage.
    a. The National Acute Spinal Cord Injury Study 2 (NASCIS 2) showed a modest but significant benefit compared with placebo for high-dose methylprednisolone if started within 8 hours of injury. The initial dose of 30 mg/kg intravenous bolus is followed by 5.4 mg/kg/hour infusion for 23 hours. Complications include pneumonia, sepsis, and gastrointestinal hemorrhage.
    b. NASCIS 3 showed an additional 24 hours of steroid infusion to be beneficial to patients who received the initial bolus between 3 and 8 hours after injury. Treatment started at later than 8 hours after injury resulted in poorer outcomes than did placebo treatment.
11. **Restoration and maintenance** of spinal alignment.

VI. SEQUELAE OF SPINAL CORD INJURIES

A. Pressure sores are the most preventable complication of spinal cord injury.

1. **Prevention.** Patient and family education are important. Pressure is relieved by turning in bed every 2 hours and "wheelchair" lifts for 5 to 10 seconds every 15 to 30 minutes. Special mattresses and wheelchair cushions do not obviate proper positioning and frequent repositioning. The skin is kept clean, dry, and inspected daily. Attention is paid to nutritional requirements.

TABLE 45.1 Expected Functional Outcomes in Spinal Cord Injury

Function	C1–C4	C5	C6	C7–C8	T1–T9	T10–S5
Respiratory	Ventilator dependent[a]	Assisted cough	Assisted cough	Assisted cough	Decreased endurance	Intact
Bowel	Total assist	Total assist	Moderate assist	Moderate assist	Independent	Independent
Bladder	Total assist	Total assist	Moderate assist	Variable assist	Independent	Independent
Bed mobility	Total assist	Some assist	Some assist	Variable assist	Independent	Independent
Transfers	Total assist	Total assist	Variable assist	Variable assist	Independent	Independent
Pressure relief, positioning	Total assist	Independent with equipment	Independent with equipment	Independent	Independent	Independent
Eating	Total assist	Independent with equipment and setup	Variable assist	Independent	Independent	Independent
Dressing	Total assist	Near total assist	Moderate assist	Variable assist	Independent	Independent
Grooming	Total assist	Moderate assist	Independent with equipment	Independent	Independent	Independent
Bathing	Total assist	Total assist	Moderate assist	Variable assist	Independent	Independent
Wheelchair	Power with special controls	Near total assist or power	Moderate assist or power	Minimal assist	Independent	Independent
Ambulation	Not indicated	Not indicated	Not indicated	Not indicated	Typically not functional	Functional with variable assist
Communication	Moderate assist with equipment	Independent with equipment	Independent with equipment	Independent	Independent	Independent
Transportation	Total assist	Highly custom van with lift	Modified van with lift	Modified vehicle	Hand controls	Hand controls
Homemaking	Total assist	Total assist	Moderate assist	Variable assist	Independent, moderate assist	Independent, minimal assist
Assist required	24 hr/d	16 hr/d	10 hr/d	8 hr/d	3 hr/d	0–2 hr/d

[a] C4 level may be ventilator independent needing assisted cough.

Data from Consortium for Spinal Cord Medicine. Outcomes following traumatic spinal cord injury: clinical practice guidelines for health-care professionals. Paralyzed Veterans of America, 1999.

TABLE 45.2 Key Muscles and Sensory Areas for Determination of Neurologic Level of Injury

Level	Muscle Action	Key Muscle	Key Sensory Area
C2	—	—	Occipital protuberance
C3	—	—	Supraclavicular fossa
C4	—	—	Top anterior shoulder
C5	Elbow flexion	Biceps brachialis	Lateral antecubital fossa
C6	Wrist extension	Extensor carpi radialis	Thumb
C7	Elbow extension	Triceps	Dorsal middle finger
C8	Finger flexion (third)	Extensor digitorum profundus	Dorsal little finger
T1	Finger abduction (fifth)	Abductor digiti minimi	Medial antecubital fossa
T2	—	—	Apex of axilla
T3	—	—	Third intercostal space
T4	—	—	Nipple line
T5	—	—	Midway between T4 and T6
T6	—	—	Xiphisternum
T7	—	—	Midway between T6 and T8
T8	—	—	Midway between T6 and T10
T9	—	—	Midway between T8 and T10
T10	—	—	Umbilicus
T11	—	—	Midway between T10 and T12
T12	—	—	Midpoint of inguinal ligament
L1	—	—	Midway between T12 and L2
L2	Hip flexion	Iliopsoas	Mid-anterior thigh
L3	Knee extension	Quadriceps	Medial femoral condyle
L4	Ankle dorsiflexion	Tibialis anterior	Medial malleolus
L5	Toe extension (first)	Extensor hallucis longus	Dorsum of foot at third metatarsophalangeal joint
S1	Ankle plantar fexion	Gastrocnemius, soleus	Lateral heel
S2	—	—	Mid-popliteal fossa
S3	—	—	Ischial tuberosity
S4-5	—	—	Perianal sensation

Data from Maynard FM, Bracken MB, Creasey G, et al. International Standards for Neurological and Functional Classification of Spinal Cord Injury. *Spinal Cord.* 1997;35:266–274.

2. **Pressure relief.** A repositioning schedule ensuring that the sore is always pressure free needs to be rigidly followed because the reduced number of possible weight-bearing position makes another sore more likely. Simultaneous management of more than one pressure sore requires special frames or flotation beds.
3. **Débridement.** Saline wet-to-dry gauze and whirlpool therapy are standard, but commercial enzyme preparations are less labor intensive. If the eschar is hard and blackened, necrotic tissue is removed surgically.
4. **Dressings.** Shallow ulcers are covered with sterile gauze. Occlusive dressings may promote more rapid healing and have to be changed less often but are much more expensive. Deeper, pear-shaped ulcers are loosely packed with saline-soaked gauze to prevent abscess formation and to promote "bottom-up" healing. The goal is to keep the wound moist, whereas the surrounding tissue is kept dry.
5. **Electrical stimulation** may accelerate wound healing.
6. **Surgical excision** with a myocutaneous flap to fill the cavity is usually required for deeper ulcers. Reduction of bony prominences may be necessary.

B. **Deep venous thrombosis** is a serious concern after spinal cord injury. Pain may not be felt below a sensory level, and swelling may be masked by edema and vasomotor changes.

1. **Prophylaxis** is needed for up to 3 months or until discharge from the rehabilitation unit. Intermittent pneumatic compression devices or compression stockings are used for the

2 weeks after injury. Anticoagulation with low-molecular-weight heparin or adjusted-dose unfractionated heparin should be started 48 to 72 hours after injury and continued 8 to 12 weeks depending on associated risk factors. Vena caval filters are placed in patients with contraindications to or who have undergone unsuccessful anticoagulation therapy. Filters should also be considered in addition to anticoagulation in the care of patients with complete C2 or C3 neurologic levels of injury.

2. **Treatment** is the same as that of patients without spinal cord injury. Mobilization and exercise of the lower extremities should be withheld 48 to 72 hours until anticoagulation is adequate. Pain relief should be provided to lessen the possibility of autonomic dysreflexia.

C. Autonomic dysreflexia. From 30% to 85% of patients with quadriplegia or high paraplegia have paroxysmal episodes of severe hypertension, sweating, flushing, and piloerection accompanied by headache, chest pain, and bradycardia or tachycardia in response to relatively benign stimuli below the level of injury. Pulmonary edema, intracranial hemorrhage, cerebral infarction, seizures, or death can result. Bladder and bowel distention, instrumentation, or irritation are the most common precipitating stimuli.

1. **Etiology.** In the setting of a spinal lesion above the major splanchnic outflow tract (T6–L2), reflex activation of sympathetic discharge occurs below the lesion unchecked by descending inhibitory pathways from supraspinal centers.
2. **Management.** Initial treatment entails removal of the precipitating stimulus and medication for the hypertensive crisis.
   a. **Removal of precipitating stimulus.**
      (1) Stop procedure.
      (2) Check for urinary catheter blockage.
      (3) Remove tight clothing, shoes, straps, and other restrictive items.
      (4) Catheterize carefully with 2% lidocaine jelly.
      (5) Perform kidney, ureter, and bladder and rectal examination with lidocaine jelly to check for impaction.
      (6) Check for sores, infection, trauma, and fractures.
      (7) Consider acute abdomen and deep venous thrombosis.
   b. **Management of hypertension.**
      (1) Elevate head of bed or place patient in sitting position to induce postural changes in blood pressure.
      (2) Drug therapy.
         (a) Nifedipine 10 mg by mouth (immediate release form—bite through capsule and swallow); monitor response *or*
         (b) Nitroglycerin 2% ointment—1 inch (2.5 cm) applied above neurologic site of injury; monitor response.
      (3) If blood pressure remains critical, intravenous protocols (e.g., hydralazine, diazoxide, and sodium nitroprusside) for hypertensive crisis must be initiated.
   c. **Management of profuse sweating without hypertension.** Give propantheline at 15 mg by mouth (may be repeated after 10 minutes) or oxybutynin at 5 mg by mouth (may be repeated after 10 minutes).
3. **Prophylactic medications.**
   a. Nifedipine 10 mg by mouth 30 minutes before procedure.
   b. Phenoxybenzamine 10 to 20 mg by mouth three times a day.
   c. Scopolamine patch may help with reflex sweating.

D. Depression must be continually assessed and managed.

E. Central pain syndrome. Development of chronic dysesthesia or central (neuropathic) pain above, at, or distal to the level of injury poses therapeutic challenges. Central pain is in addition to the musculoskeletal and visceral pain experienced by patients with spinal cord injuries.

1. **Etiology.**
   a. Above level of injury. Compressive mononeuropathy (e.g., ulnar and median) and post-traumatic syringomyelia formation.
   b. At level of injury. Central pain from cord damage, radicular pain from root damage, and complex regional pain syndrome.
   c. Below level of injury. Central pain.

2. **Pharmacologic approach** is trial and error.
   a. **Tricyclic antidepressants** for nonlancinating pain.
      (1) Amitriptyline (Elavil) or nortriptyline (Pamelor) 10 to 25 mg by mouth at bedtime; increase by 10 to 25 mg every 5 to 7 days as tolerated to 75 to 150 mg at bedtime.
      (2) Side effects include sedation, anticholinergic effects, orthostatic hypotension, weight gain, and cardiac arrhythmia.
      (3) If side effects are not tolerable, a chemically unrelated compound, such as duloxetine (Cymbalta) at 30 to 60 mg per day by mouth, may be tried.
   b. **Anticonvulsants** (frequently in combination with tricyclic antidepressants) for lancinating central pain.
      (1) Carbamazepine (Tegretol) 100 mg twice a day increased 100 mg every 3 days as tolerated to a serum level of 8 to 10 mg per ml in three or four doses per day.
         (a) Side effects include sedation, diplopia, gastrointestinal upset, ataxia, weakness, rash, and bone marrow suppression.
         (b) Monitor CBC with platelets every 2 weeks for 3 months, then CBC, platelets, and liver function every 3 to 6 months.
      (2) Gabapentin (Neurontin) 100 mg three times a day increased 100 to 300 mg every 3 days as tolerated up to 600 to 900 three or four times a day.
         (a) Side effects include drowsiness and dizziness.
         (b) Blood levels are not used clinically, and no monitoring is needed.
      (3) Pregabalin (Lyrica) 50 mg three times a day increased to 100 mg three times a day after 1 week as tolerated.
         (a) Side effects include peripheral edema, weight gain, constipation, dizziness, and somnolence.
         (b) Blood levels are not used clinically and no monitoring is needed.
3. **Physical methods** may provide some temporary relief for central pain at the level of the injury.
   a. Transcutaneous electrical nerve stimulation.
   b. Warm or cool packs and ultrasound.
4. Surgical treatment should be considered only after conservative therapy has failed.
   a. Dorsal root entry zone (DREZ) surgery.
      (1) Laminectomy and radiofrequency ablation of DREZ is performed two levels above and one level below the site of injury.
      (2) Improvement is realized in 60% to 90% of patients. Best results are achieved in patients with pain at or just below the level of injury.
      (3) Complications include loss of one or two sensory levels, CSF leakage, hematoma, and bowel, bladder, and sexual dysfunction.
   b. Avoid sympathectomy, rhizotomy, and cordotomy.
5. **Narcotic therapy** is indicated only after both conservative and surgical therapies have failed.
   a. Combination with tricyclic antidepressants may be synergistic.
   b. The patient must be carefully selected and carefully supervised.
   c. Methadone (Dolophine) sustained release oxycodone (Oxycontin), and an intrathecal morphine pump (if possible) are options for selected patients.
      (1) A formal contract detailing expectations and criteria for termination of treatment are made with the patient.
      (2) Periodic attempts should be made to wean the medication.
      (3) Side effects include sedation and cognitive slowing, respiratory depression, constipation, and reduced sexual function.

VII. SPINAL EPIDURAL ABSCESS

A. Etiology. Epidural abscesses occur in patients with predisposing conditions, such as a chronic disease (alcoholism and immunodeficiency states), a spinal abnormality or intervention, or a source for local or systemic infection. Bacteria seed the epidural space by

either contiguous spread or hematogenous dissemination. *Staphylococcus aureus* accounts for 60% of cases, whereas other gram-positive cocci account for 13% and gram-negative bacteria occur in about 15% of cases.

B. Clinical features. Back pain, fever, and neurological deficits are the most common symptoms; however, this triad is not often found in all patients. The clinical features are divided into four stages:

1. Back pain at the level of the abscess.
2. Radicular pain from the involved level of the spinal column.
3. Motor weakness, sensory deficit, and bowel and bladder dysfunction.
4. Paralysis.

The rate of progression between stages can vary between a few hours to days.

C. Diagnosis. Two-thirds of patients will have a leukocytosis. The vast majority of patients will also have an elevated erythrocyte sedimentation rate upon presentation. CRP levels are also useful, but processing can take hours to days, which may unnecessarily delay the diagnosis. The initial CRP value is useful for comparison to repeat values as a measure of treatment response. Bacteremia can be detected in up to 60% of cases. However, definitive diagnosis is best established by contrast-enhanced MRI of the affected area.

D. Treatment. Emergent surgical decompression and debridement combined with systemic antibiotics for at least 6 weeks is the treatment of choice. The most common causative organism is *S. aureus* (up to 70% of cases). Empiric antibiotic therapy should provide coverage against staphylococci and gram-negative bacilli.

E. Prognosis. Prompt diagnosis and the patient's neurologic status prior to surgical drainage are the most important predictors of outcome.

VIII. DEMYELINATING LESIONS OF THE SPINAL CORD

The most common cause of demyelination in the spinal cord is multiple sclerosis (MS). Up to 50% of cases will involve the spinal cord. The lesions are typically dorsolateral, longitudinal, and flame-shaped. Another less common cause of demyelination in the spinal cord is neuromyelitis optica (NMO) or Devic's disease. It is currently recognized as its own distinct disorder, separate from MS. Newly proposed diagnostic criteria for NMO include optic neuritis, acute myelitis, and at least two of the three following supportive criteria: (1) contiguous spinal cord MRI lesion extending three or more vertebral segments (Fig. 45.2), (2) brain MRI not meeting diagnostic criteria for MS, and (3) NMO-IgG seropositivity. The NMO-IgG antibody has a sensitivity of 74% and a specificity of >90%. Treatment of acute attacks of optic neuritis or myelitis often only partially respond, or do not respond at all to high-dose glucocorticoids. In this setting, plasmapheresis is often used. Maintenance of remission in NMO requires long-term immunosuppressive therapy. There has been evidence for the use of azathioprine, methotrexate, mitoxantrone, mycophenolate mofetil, and rituximab.

IX. CENTRAL CORD SYNDROME

A. Etiology. Hyperextension injuries may produce a spinal cord contusion primarily affecting the central gray matter. Lamination of tracks in the cervical cord (sacral fibers, lateral; cervical fibers, and medial) explains the clinical signs and symptoms.

B. Clinical features. Patients have "inverted quadriparesis," in which upper-extremity weakness exceeds lower-extremity weakness. Transient burning dysesthesia in the hands with little weakness, or urinary dysfunction can also occur. With recovery, the leg, bladder, and upper-extremity weaknesses improve. The fingers are last to recover.

C. Treatment.

1. **Conservative therapy** consists of rigid immobilization of the neck, physical therapy, and consideration of a course of corticosteroids.
2. **Surgical therapy.** On the basis of neuroimaging findings, patients whose condition has not improved or has plateaued or who have instability of the spine are considered for surgical decompression.

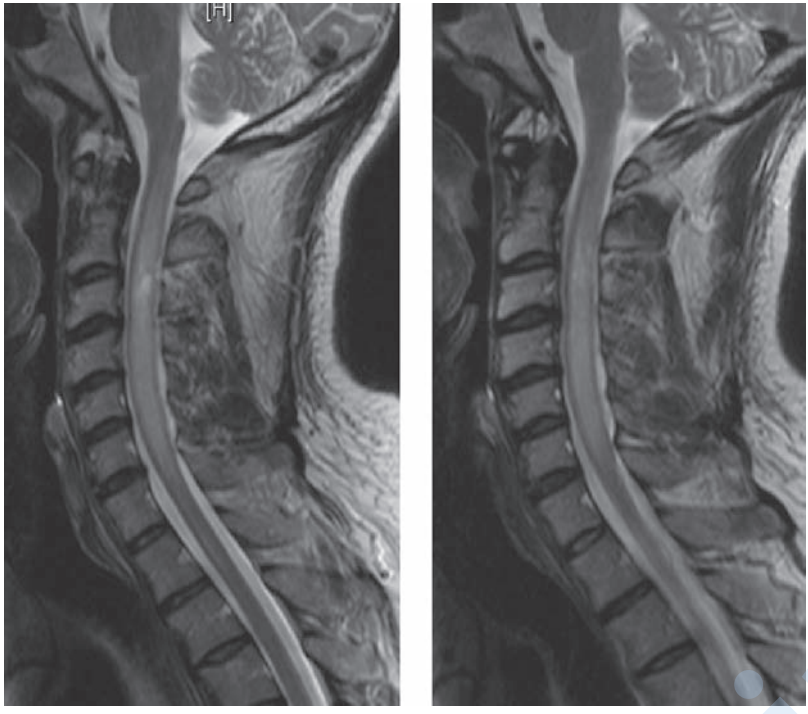

FIGURE 45.2 A 44-year-old African American man with neuromyelitis optica (Devic's disease). MRI of the cervical spine without and with contrast shows contiguous cord signal abnormality identified involving the cervical spinal cord from the craniocervical junction to the C6–C7 level. The spinal cord signal abnormality involves nearly the entire central spinal cord symmetrically with relative sparing of the lateral portions bilaterally. The cervical spinal cord signal abnormality is associated with tapered cord expansion resulting in circumferential, partial to complete effacement of the thecal sac at the involved levels. (Courtesy of José Biller)

D. Prognosis. Almost all patients have improvement, but often to an incomplete degree among the elderly. Delayed progressive myelopathy can develop in approximately 25% of cases.

X. HYPEREXTENSION–FLEXION INJURY (WHIPLASH INJURY)

A. Etiology. Automobile accidents account for approximately 85% of whiplash injuries. The cardinal symptoms of neck pain and headache are musculoskeletal. Concomitant symptoms may include dizziness, visual impairments, nausea, tinnitus, deafness, paresthesias, lower back pain, arm or shoulder pain, post-traumatic stress disorder, and cognitive dysfunction. The roles of mild CNS injury and psychosocial factors are controversial and have led to biopsychosocial models of outcome in the disorder.

B. Prevention. Automobile head restraints reduce flexion–hyperextension motion of the head in automobile accidents, especially during rear-end collisions. However, surveys have shown that the restraints frequently are adjusted incorrectly.

C. Natural history. Rear-end collisions are involved in most whiplash injuries. Cynicism and controversy exist over the cause of chronic whiplash syndrome. Although figures vary widely, approximately 15% to 30% of patients continue to have symptoms 6 months after the injury. By 12 months, 80% of patients have no symptoms, whereas

5% of patients remain severely affected. Results of fluoroscopically guided nerve block studies suggest that zygapophyseal joint pain (usually C2–C3) accounts for 50% of chronic neck pain after whiplash.

D. Treatment. Compensation concerns hinder controlled clinical trials of treatment.

1. Positive attitude and encouragement.
2. Ice for first 24 hours.
3. Muscle relaxants, nonsteroidal anti-inflammatory drugs, and adequate pain relief in the first 7 to 14 days.
4. Resumption of most normal activities together with active therapy or home exercises results in better outcome than with conventional regimens of restricted activity, rest, and soft cervical collar.
5. Heat, ultrasound, massage, and trigger-point injections often make patients more comfortable but remain unproven.
6. Percutaneous radiofrequency neurotomy for cervical zygapophysial joint pain has been showed to be effective in several studies, but the pain frequently returns and necessitates repeated procedures.

XI. SPASTICITY

Spasticity is one of the cardinal manifestations of chronic spinal cord disease. In acute spinal lesions, spasticity develops after a variable period of spinal shock, whereas in disorders with insidious onset, it may be the first symptom noticed.

A. The decision to treat a patient must be made on an individual basis. Treatment is indicated when the advantages of spasticity outweigh the disadvantages. Specific treatment goals need to be formulated.

1. **Advantages.**
   a. Bowel training maintains sphincter tone.
   b. "Internal crutches" are available for ambulation.
   c. Weight bearing is possible in transfers.
   d. Osteopenia is reduced.
   e. Muscle bulk is increased.
   f. Venous tone is increased, and deep venous thrombosis may be decreased.
2. **Disadvantages.**
   a. Pain and falls result from paroxysmal spasms.
   b. Hygiene is impaired owing to hip adductor spasticity.
   c. Joint contractures occur.
   d. Pressure sores form.
   e. Renal damage occurs because of external sphincter spasticity.
   f. Movements required for activities of daily living are impaired or interrupted.

B. Assessment of severity can be made with the modified Ashworth scale (Table 45.3).

C. A **changing pattern in a previously stable degree of spasticity** should alert the clinician to varying etiologic factors.

1. Medication: fluoxetine, sertraline, or trazodone.
2. Anxiety.
3. Tight clothing or shoes.
4. Inadequate or prolonged postures.
5. Formation of pressure sores.
6. Development of deep venous thrombosis.
7. Ingrown toenails.
8. Spinal instability.
9. Fractures.
10. Post-traumatic syringomyelia.
11. Gastrointestinal dysfunction: impaction, hemorrhoids, and acute abdomen.
12. Genitourinary dysfunction: infection, stones, blocked catheters, and disorders of testicle, prostate, vagina, uterus, or ovary.

D. Management is based on a multidisciplinary approach with a rigorous program of both passive and active stretching.

TABLE 45.3 Modified Ashworth Scale for Measuring Spasticity

Grade 0: Normal muscle tone
Grade 1: Slight increase in muscle tone; "catch" or minimal resistance at end of ROM
Grade 2: Slight increase; "catch" followed by minimal resistance for remainder of ROM
Grade 3: More marked increase in tone through most of ROM; parts moved easily
Grade 4: Considerable increase in tone; passive movement difficult
Grade 5: Affected part or parts rigid in flexion or extension
Total score is the average of bilateral hip flexion and abduction, knee flexion, and ankle dorsiflexion.

Abbreviation: ROM, range of motion.

Adapted from McLean BN. Intrathecal baclofen in severe spasticity. *Br J Hosp Med.* 1993;49:262–267.

1. **Physical modalities**.
   a. Range of motion and stretching exercises.
   b. Heat or cold.
   c. Vibration (increases presynaptic spinal inhibition).
   d. Splints, casts, and orthotics to prevent contractures and increase mobility.
2. **Useful medications** are summarized in Table 45.4. Muscle relaxants (antispasmodics) are not used in the long-term management of spasticity.
3. **Nerve blocks**.

Botulinum toxin type A (Botox; Allergan, Irvine, CA, USA) injection has been found effective for focal spasticity at a variety of sites.

   a. The discomfort and expense of numerous injections in large lower extremity muscles limit this technique to relatively small muscles.
   b. Transient postinjection discomfort and side effects are generally well-tolerated. Excessive weakness and flu-like syndromes may be experienced at initiation of treatment. Botulinum injections should be avoided by patients receiving aminoglycosides. Neutralizing antibodies are more common with larger, more frequent doses.
   c. Advantages are reversible block (2 to 6 months) and selectivity toward motor fibers.
   d. Disadvantages are expense and need for repeated injections.
4. **Neurosurgical procedures**.
   a. An **intrathecal baclofen pump** is a safe alternative to ablative surgery for intractable spasticity at experienced centers.
      (1) Referral to an experienced center should be considered for patients with stable neurologic disorders accompanied by spasticity seriously interfering with quality of life. Oral agents should have been found ineffective or limited owing to intolerable side effects.
      (2) Patients are selected after a test dose of 50 to 75 mg baclofen administered by lumbar puncture. Spasticity is assessed 1, 2, 4, and 8 hours after injection with the modified Ashworth scale (Table 45.3). If two-point improvement is not documented and side effects are tolerable, a second larger test dose (75 to 100 mg) is given the next day.
      (3) During the first year after implantation, daily doses generally increase before stabilizing in the range of 300 to 800 mg per day.
      (4) Improvement is observed in muscle tone, mobility, and bladder function, and spasms and musculoskeletal pain are relieved. There is little or no relief of central pain.
      (5) Systemic side effects are less than with oral therapy. Drowsiness, nausea, hypotension, headache, and weakness may be experienced during the dose titration phase. Infections and catheter or pump complications are rare but potentially serious side effects.
      (6) Depletion of the pump battery in 5 to 7 years necessitates replacing the entire pump unit.

TABLE 45.4 Drug Management of Spasticity

Drug	Daily Dosage[a] (Starting Dosage)	Side Effects and Comments
Baclofen (Lioresal; Novartis, Hanover, NJ, USA)	10–160 mg (5 mg b.i.d.)	Drowsiness, weakness, tremor, ataxia, abrupt withdrawal with seizures, confusion, hallucinations
Tizanidine (Zanaflex; Athena Neurosciences, Inc., San Francisco, CA, USA)	8–32 mg (2 mg at bedtime)	Use with caution in liver disease Dry mouth, sedation, dizziness, risk of hypotension, insomnia, hallucinations, hepatotoxicity Liver monitoring at 1, 3, and 6 mo Somewhat less weakness than with baclofen
Gabapentin (Neurontin; Parke-Davis, Morris Plains, NJ, USA)	300–3,600 mg (100 mg t.i.d.)	Nausea, sedation, ataxia, dizziness
Diazepam (Valium; Roche Products, Nutley, NJ, USA)	4–60 mg (2 mg at bedtime)	Sedation, cognitive changes, depression, weakness, dependence, abuse, withdrawal syndrome
Dantrolene[b] (Dantrium; Procter and Gamble Pharmaceuticals, Inc., Cincinnati, OH, USA)	25–400 mg (25 mg once a day)	Weakness, hepatotoxicity, confusion, sedation, nausea, diarrhea Monitor liver function closely

[a]It is important to start with a low dosage and gradually build to a target dosage as tolerance of the sedation and most other side effects of the medication develops.

[b]The potentially fatal hepatotoxicity of dantrolene is more common among adults and those taking estrogens. This drug probably should be avoided by those with preexisting liver disease.

Abbreviations: b.i.d., twice a day; t.i.d., three times a day.

(7) Although life-threatening, all instances of drug overdose have been completely reversible. Experience and better pump design have decreased the complication rate to <5%. In early series of patients, surgical revision was needed in 20% of cases for catheter-related problems.

b. **Selective posterior rhizotomy** with intraoperative EMG selection of lumbosacral rootlets for sectioning is useful in the management of cerebral palsy. Two-thirds of patients' conditions are improved with minimal sensory loss and few side effects. DREZ operations are functionally similar microsurgical procedures.
c. Percutaneous posterior rhizotomy is technically more difficult, and recurrence may be more of a problem.
d. Efficacy of spinal cord stimulators is controversial.
e. Peripheral neurectomy is occasionally used to relieve specific joint contractures.
f. Longitudinal myelotomy, nonselective posterior rhizotomy, and anterior rhizotomy are rarely performed.

5. **Orthopedic procedures** are used most often performed in a supportive role to relieve pain, increase mobility, and decrease deformity in cerebral palsy.
   a. Tendon release, lengthening, and transfer.
   b. Osteotomy and arthrodesis.

Recommended Readings

Belanger E, Levi AD. The acute and chronic management of spinal cord injury. *J Am Coll Surg.* 2000;190:603–618.
Bryce TN, Ragnarsson KT. Pain after spinal cord injury. *Phys Med Rehabil Clin N Am.* 2000;11:157–168.
Darouiche RO. Spinal epidural abscess. *N Engl J of Med.* 2006;355:2012–2020.
Davis EC, Barnes MP. Botulinum toxin and spasticity. *J Neurol Neurosurg Psychiatry.* 2000;69:143–147.

Green R, Kinsella LJ. Current concepts in the diagnosis of cobalamin deficiency. *Neurology.* 1995;45:1435–1440.
Kita M, Goodkin DE. Drugs used to treat spasticity. *Drugs.* 2000;59:487–495.
Kumar N. Copper deficiency myelopathy. *Mayo Clin Proc.* 2006;81(10):1371–1384.
Maynard FM Jr, Bracken MB, Creasey G, et al. International Standards for Neurological and Functional Classification of Spinal Cord Injury. American Spinal Injury Association. *Spinal Cord.* 1997;35:266–274.
Milhorat TH, Chou MW, Trinidad EM, et al. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. *Neurosurgery.* 1999;44:1005–1017.
Newey ML, Sen PK, Fraser RD. The long-term outcome after central cord syndrome: a study of the natural history. *J Bone Joint Surg Br.* 2000;82:851–855.
Shamji MF, Ventureyra EC, Baronia B, Nzau M, Vassilyadi M. Classification of symptomatic Chiari I malformation guide to surgical strategy. *Can J Neurol Sci.* 2010;37:482–487.
Teasell RW, Mehta S, Aubut JA, et al. A systematic review of pharmacologic treatments of pain after spinal cord injury. *Arch Phys Med Rehabil.* 2010;91:816–831.
Tompkins M, Panuncialman I, Lucas P, et al. Spinal epidural abscess. *J Emerg Med.* 2010;39(3):384–390.
Van Suijlekom H, et al. Whiplash-associated disorders. *Pain Practice.* 2010;10(2):131–136.

CHAPTER

46 Peripheral Neuropathy

John C. Kincaid

Peripheral neuropathy is the general term for diseases that affect the peripheral nervous system. The primary sites of pathology are the cell bodies, the axons, and the myelin sheath. Terms used to describe peripheral lesions, in a proximal to distal sequence, are as follows:

Neuronopathy: abnormality of the nerve cell body, usually producing motor, sensory, or autonomic dysfunction independently.

Radiculopathy: abnormality at the level of the nerve root, usually at a single spinal level and most often due to compression by a herniated disc or osteophyte.

Polyradiculopathy: abnormality involving the nerve roots at many spinal levels and most often caused by inflammation, infection, or infiltration by neoplastic cells.

Plexopathy and plexitis: abnormality affecting the brachial or lumbosacral plexus. Plexopathy is the more general term while plexitis implies an inflammatory etiology.

Polyradiculoneuropathy: abnormality at both the nerve roots and the peripheral nerve trunk level.

Polyneuropathy: abnormality of multiple peripheral nerve trunks, usually presenting in a length dependent symmetrical pattern.

Axonal neuropathy: neuropathy in which the primary site of pathology is the axons. Conduction studies show loss of response amplitudes and mild velocity slowing.

Demyelinating neuropathy: neuropathy in which the primary site of pathology is the myelin sheaths. The conduction study parameters listed are the standard electrophysiological definitions of demyleinating neuropathy.

Mononeuropathy: abnormality of an individual peripheral nerve trunk most often due to entrapment or local trauma.

Mononeuritis multiplex: abnormality of multiple, individual nerves trunks occurring in a serial fashion most often due to vasculitis affecting the vasa nervorum.

I. SYMPTOM BASED MANAGEMENT

Whether or not the specific cause of a neuropathy is known and a specific treatment is available, the patient often reports a group of symptoms that are relatively similar. Following a standard approach to management of these symptoms is useful. Neuropathic symptoms may include the following:

Pain
Paresthesias
Sensory loss
Weakness
Cramping
Unstable balance

A. Pain is often the most bothersome symptom and may have several different characters. The paradigm described below is based on symptomatic treatment of painful diabetic neuropathy but should be applicable to other neuropathies.

1. **Fiery, burning pain** (or cold, frostbite-like pain) is more felt in the toes, bottoms of the feet, and fingertips. If the symptom is bothersome enough for the patient to request treatment, an antiepileptic medication such as gabapentin should be tried first. An initial dose of 300 mg once or twice daily is reasonable. If a benefit is going to occur, some

improvement often begins within a day or two of starting the medication. The dosage may need to be increased to three times daily if symptoms are re-exacerbated before the next dose. The dose can be increased at weekly intervals to optimize the response but doses above 2,400 mg per day often provide no further benefit. Full relief of symptoms is often not achievable. Pregabalin may also provide symptomatic relief. This drug is only approved for use in symptomatic diabetic neuropathy and post-herpetic neuralgia but may help symptoms in other neuropathies. Approval for payment by insurance often limits the ability to use this medication. Mild analgesics such as aspirin or acetaminophen can help relieve low-level pain. Nonsteroidal anti-inflammatory drugs usually do not help this type of pain but can be tried.

Burning pain can often be improved by tricyclic antidepressants. Medications such as amitriptyline, nortriptyline, desipramine, and doxepin are the preferred agents. Antidepressants of the selective serotonin reuptake inhibitor class do not seem to provide much pain-modulating benefit but can be tried. When starting one of the tricyclic medications, inform the patient that side effects such as morning sedation, dry mouth, and blurred vision may occur. These effects usually lessen within a few days. Start these medications at a low dosage, such as 25 mg an hour before bedtime. Benefit may begin within a few days but may take several weeks to become evident. Increase the dosage by 10 to 25 mg every 1 to 2 weeks if there has been no benefit at the initial dosage, or if the pain intensity worsens after initial improvement. A dose of 35 to 75 mg is usually sufficient, but higher amounts can be used within the bounds of the particular drug. If a medication is beneficial, it should be continued for at least 6 months. At that point, a taper of 10 to 25 mg should be tried to determine whether the drug is still providing benefit. If symptoms worsen, the drug should be returned to the previous level. Long-term use may be needed. Newer antidepressant agents like duloxetine, which is approved for diabetic neuropathy, may help with this type of pain and have fewer side effects than the tricyclic drugs.

Pain not responsive to the agents above may require stronger analgesics such as tramadol, codeine, hydrocodone, or oxycodone in combination with acetaminophen. Longer-acting opioids such as sustained-release oxycodone, morphine, or methadone may provide smoother pain control for patients with severe discomfort. Methadone is the least expensive of these. Doses as low as 5 mg twice a day may help but up to 20 mg four times daily may be required for severe pain. It is important for the patient and physician to understand that even major analgesics will not usually provide complete pain relief. Achieving mild to moderate relief is a reasonable goal. Neuropathic pain is often worse when the patient retires for sleep, and, if possible, the stronger analgesics should be reserved for that time.

Topical capsaicin creams also may be helpful for this type of pain. Depletion of neurotransmitters in pain-sensing neurons is the proposed mechanism of action. These preparations are applied to the painful areas three or four times a day. Several weeks are required for benefit to appear, and a short-term increase in the pain may occur before the benefit begins. This medication is somewhat cumbersome to use. Topical lidocaine patches may be helpful if the pain is localized. Like the other interventions, they may lessen but will not eliminate the pain.

2. **Short electric-like jabs of pain** are another form of neuropathic pain. These are often felt in the toes, feet, lower legs, or fingers. Each lasts a second or two, and tends to migrate from one site to another. The patient may yell or gasp due to the intensity of the pain. This type of pain often responds to gabapentin or pregabalin. Other anticonvulsant drugs such as phenytoin at 100 mg two or three times a day or carbamazepine at 100 mg twice a day up to 200 mg three times a day may help. Benefit from any of the medications often begins within a few days. The dosage may need to be increased if the initial benefit lessens. Monitoring of drug levels is probably not helpful in maximizing benefit. CBC should be monitored for patients undergoing maintenance therapy with carbamazepine.
3. **Tight or band-like pressure pain** in the feet or lower parts of the legs is resistant to symptomatic treatment. Encourage patients not to rely on medication to provide relief from this type of pain.

4. **Allodynia,** pain to non-noxious stimuli, often is an accompaniment to spontaneous pain. The patient perceives light touch in the involved area as exquisitely uncomfortable during and a few seconds after the touch. Wearing light cotton socks or gloves can lessen these sensations, as can tents in the foot end of the bed linens to keep the toes from being touched. The antidepressants discussed above may improve these sensations.

B. Paresthesia is another form of sensory abnormality. This phenomenon takes the form of feelings of repetitive prickling, or "pins and needles" sensations. These sensations are felt in larger areas than the discrete sharp jabs of pain discussed in I.A.2. and may be felt in the toes, the feet, or the hands. They occur spontaneously or may be produced by touching of the body part. These sensations tend to improve with antiepileptic medications discussed above. Lessening of the intensity and frequency should be the goal of treatment rather than complete relief. Analgesics do not help these symptoms.

C. Sensory loss can cause the affected areas to feel "dead, like blocks of wood or leathery." Sensations such as these do not respond to symptomatic treatment. Because of the loss of sensation underlying these symptoms, it is important for the patient to visually inspect the bottoms of the feet at least twice daily for local trauma such as blisters or cuts. Unrecognized lesions may lead to more serious problems such as ulcers and infections. Properly fitting shoes are important.

D. Weakness can occur focally in radiculopathy, plexopathy, mononeuropathy, or polyneuropathy. Bracing with an orthotic may partially compensate the deficit while recovery is awaited. Mobilization of the weak body part through a complete range of motion should be done at least daily to prevent contracture formation.

1. Patients with polyneuropathy tend to have **distal, symmetric weakness.** Weakness limited to the intrinsic foot muscles manifesting as difficulty abducting the toes is not clinically significant. Spread of the deficits to the toe extensors or flexors, or particularly the ankle musculature can impair balance. Ankle–foot orthotics may greatly improve standing and walking stability. Use of large-handled utensils may help compensate for finger and hand weakness. Physical and occupational therapy can help the patient maximize function.
2. **Proximal, symmetric weakness** in the legs causing difficulty in getting up from chairs or with stairs, or of arm weakness causing lifting difficulty is relatively distinct and most often suggests inflammatory demyelinating neuropathy (Guillain–Barré syndrome or its chronic variants).
3. **Unilateral proximal leg weakness** can occur in lumbar plexopathy, such as diabetic amyotrophy. Knee weakness can predispose patients to falling. Patients compensate by keeping the knee locked in extension. Minor dislodgment from that position, caused by a shift in body position or a slight bump from a passerby, exposes the weakness. Successful bracing of this joint is more difficult than at the ankle. A lift chair may help with getting up from a sitting position. Evaluation by a physical therapist and a physical medicine rehabilitation physician can be very helpful in optimally managing all of these situations.

E. Cramping can be a bothersome component of peripheral neuropathy. Intrinsic foot and leg muscles like the gastrocnemius and hamstrings are the more common sites. Cramps may be provoked by movement or occur spontaneously. Successful treatment can be a challenge. Maintenance of proper hydration and serum potassium levels are important first steps. Use of quinine sulfate before bedtime has been the traditional mainstay of symptomatic treatment for prevention of nocturnal leg cramps. The 260 mg over-the-counter preparation was withdrawn by the U.S. Food and Drug Administration over concern for rare but potentially serious, unpredictable adverse hematological or other type events. Despite its long-time use and anecdotal support, no clinical study done to modern levels of design rigor is available to support quinine's use. A 325 mg preparation is still available by prescription but is only approved for treatment of malaria. No other medication is currently approved for the treatment of this bothersome symptom. Traditional muscle relaxers do not help. Low doses of benzodiazepines like diazepam or clonazepam can be tried.

F. Unstable balance can arise from sensory loss, cerebellar dysfunction, or weakness in the legs. Mild imbalance may require no active management other than caution on the

patient's part. More pronounced deficits that put the patient at risk of falling require intervention. The intervention can be informal such as another person's arm to hold, strategically placed furniture, or use of a shopping cart at the store. More formal aids include a cane, walker, wheelchair, or motorized scooter. Patients may have increased difficulty in darkness or in situations in which their eyes are temporarily closed, such as showering. A patient who has had several falls should be encouraged to use a wheelchair to avoid further injury. A physical medicine rehabilitation evaluation can help determine the best management.

II. DIAGNOSIS AND MANAGEMENT OF SPECIFIC CONDITIONS

Autoimmune Inflammatory Neuropathies

A. Acute inflammatory demyelinating neuropathy (Guillain–Barré syndrome).

1. **Clinical features.** This disorder manifests as weakness and sensory loss, usually beginning in the feet and then spreading into the legs and arms. The onset may follow a viral or other infectious-type illness by a week or 2, but can also develop spontaneously. The condition evolves and usually reaches maximum severity by 4 but not more than 8 weeks. The maximum impairment may be mild or progress to paralysis and need for ventilation. Weakness is usually the cause for the patient seeking medical attention. Loss of muscle stretch reflexes is an expected finding. Sensory deficits tend to be mild.
2. **Laboratory findings** of increased CSF protein concentration along with a normal or minimally elevated WBC count support the diagnosis. Nerve conduction studies that show slowing of velocity to <70% of normal or prolongation of distal latencies to >125% to 150% of normal support the diagnosis but this "demyelinating" pattern may not always be found. Screening for arsenic intoxication and acute intermittent porphyria should be performed because these disorders can produce a similar clinical picture. Tick bite paralysis also can mimic this condition.
3. **Treatment.** Patients with this working diagnosis should be admitted to a hospital. Mild cases may not need active intervention but should be observed closely for at least several days to ensure the deficits have stabilized. Weakness of a degree that impairs walking or use of the arms justifies active treatment. At least two-thirds of patients will have to follow a spontaneously improving course. Two treatments—plasmapheresis and intravenous gamma globulin infusion—have shown benefit of shortening the duration of the weakness. Better benefits tend to result if treatment is begun within the first week or two of onset.
   a. **Plasmapheresis,** also called **plasma exchange,** is done by removing a portion of the plasma to eliminate components, as yet undefined, that are the mediators of the attack. The treatment usually consists of five exchanges done on every other day schedule. Vascular access through peripheral veins may be possible, but a central line is usually required. Treatments are generally well tolerated. Transient hypotension can occur, and therefore this mode may not be optimal for patients with labile cardiovascular systems.
   b. **Intravenous gamma globulin infusion** is most commonly done on a 0.4 g/kg/day 5 days schedule. The total target dose of 2 g per kg can also be given on a more compressed schedule. This treatment has been shown to be equally effective to plasmapheresis and is often logistically easier. Headache and puritus are the more common side effects of the infusions. Major complications are infrequent but have included vascular occlusive incidents, which are presumed to be secondary to hyperviscosity due to the large protein infusion.
   c. **With either treatment,** improvement may begin within as early as a few days but may not appear for weeks and then only manifest as a shortened overall duration of the illness. Lack of improvement over the first week or so of treatment is not a valid reason to switch from the initially chosen treatment method to another. About 10% of the patients whose condition improves with treatment may have a partial relapse within a few weeks. In such instances, another one or two plasma exchanges or

gamma globulin infusions will usually reestablish the improvement. Major improvement occurs in a high percentage of patients, but even with these treatments, some patients still have a prolonged course necessitating weeks if not months of hospitalization. In more severe cases some degree of distal weakness, sensory loss, and paresthesia may persist.

Corticosteroids do not benefit patients with the acute form of inflammatory demyelinating neuropathy.

B. Chronic inflammatory demyelinating neuropathy.

1. **Clinical features.** The neuropathy is similar to the acute form described above but has a slower evolution that extends over at least 8 weeks and more commonly over many months. This condition does not often improve without active treatment. The laboratory and nerve conduction results are similar to those of the acute form. Monoclonal gammopathy of the IgM type can produce a very similar neuropathy, and evaluation should include a serum protein electrophoresis. If an IgM protein is found, a myelin-associated glycoprotein antibody test should also be performed because the presence of this antibody strongly supports the gammopathy being the cause of the neuropathy.
2. **Treatment.** The options are the same as for Guillain–Barré syndrome with the exception that corticosteroids can also be an effective intervention. Intravenous gamma globulin infusion or plasmapheresis are the more commonly chosen of the options. The schedules in II.A.3.a. for Guillain–Barré syndrome should be followed. If steroid treatment is chosen, prednisone at 1 mg per kg a day can be used. If the initial treatment is going to help, some signs of improvement should be evident within 1 month of initiation. Further improvement is then likely over the next few months. If steroids are chosen, a tapering schedule of 10 mg per month can be followed after the initial 4- to 6-week period of 1 mg per kg dosing. If worsening occurs after a dose decrease, an increase back to the previous effective dose should be made. After a dose decrease, some steroid-treated patients report symptoms of general aching, stiffness, and listlessness. These types of symptoms are not usually due to true exacerbation and are only nonspecific symptoms from the steroid dose decrease. These type symptoms improve 2 to 3 weeks after the dose decrease. If no true improvement has occurred within the 4 to 6 weeks of treatment, benefit is unlikely, and the medication should be tapered off completely over a few weeks. Treatment with steroids is much less expensive than plasmapheresis or gamma globulin infusion but long-term steroid side effects are factors in the decision about treatment type. Patients who show a good initial response to gamma globulin infusion or plasmapheresis may need recurring treatment. Re-exacerbation within 4 to 8 weeks of the initial treatment dictates retreatment. One to 2 days of pheresis or intravenous immune globulin should be repeated and the patient observed for the next month. The need for further treatment is then dictated by re-exacerbation versus sustained improvement. In some patients recurring treatment every 3 to 6 weeks may be required to maintain the improvement. If the patient has shown sustained improvement after several repeated treatment sessions, lengthening the interval between treatments, or not retreating unless definite worsening occurs, should be considered because remission is possible. The role of other immune suppressants like azathiorprine, mycophenolate, and rituximab have not been established in the longer term treatment of this condition.

C. Vasculitic neuropathy occurs due to inflammation of the vasa nervorum. The vasculitis is usually a component of a more generalized systemic disease but in rare cases may be limited to the peripheral nerves alone.

1. **Clinical features.** The presentation and evolution of this type of neuropathy tend to be unique. Progression occurs in a patchy manner such that a single nerve in a limb malfunctions and then a nerve in another location does the same. Individual deficits often appear rather suddenly, and then accumulate over days to weeks. This stepwise and cumulative pattern is termed mononeuritis multiplex. If left unchecked, the condition often evolves into generalized, symmetric polyneuropathy. Careful history taking identifies the stepwise pattern of progression.

Vasculitic neuropathy can be serious and usually continues to progress unless treated. The neuropathy may occur in association with polyarteritis nodosa, rheumatoid arthritis, systemic lupus erythematosus, or Wegener's granulomatosis and may be a

presenting feature of these conditions. It may also occur in isolation and is then termed non-systemic vasculitic neuropathy.

2. The **diagnosis** is supported by results of laboratory studies that identify any of the aforementioned systemic illnesses. Electromyography can help by showing a patchy "axonal" type pattern of involvement. Biopsy of a peripheral nerve in an area of clinical involvement, such as the sural or a superficial radial nerve, establishes the diagnosis if the results are positive.
3. **Treatment** requires **immunosuppressive therapy.** Prednisone at 1 mg per kg a day is the initial treatment, but an additional agent like **cyclophosphamide** will likely be required for sustained benefit. Cyclophosphamide should be given by physicians familiar with its use. It can be administered by means of daily oral dosage or monthly intravenous pulses. The initial response to treatment declares itself as a cessation of further worsening. Improvement requires axonal regeneration and occurs over months to several years. Severely affected areas may show persistent deficits despite overall improvement.

D. Brachial plexitis, also known as **Parsonage–Turner syndrome** or **neuralgic amyotrophy,** is easily diagnosable once it is fully manifest but can be difficult to differentiate from cervical nerve-root compression or intrinsic shoulder disease in its early stages. Brachial plexitis can be idiopathic or may appear a few weeks after an infection or immunization. Surgery, which can be on structures remote from the shoulder, can also provoke an attack. A dominantly inherited familial form is also known. The upper trunk of the brachial plexus tends to be most often involved.

1. **Clinical features.** Pain is the initial symptom. This begins in the neck, shoulder, or upper arm. It has a constant "deep in the bone" character and is usually unilateral. The pain intensifies over days to weeks and can become excruciating. Neck movement tends not to greatly worsen the pain, but arm or shoulder motion may. Several weeks after the onset of pain, symptoms of sensory loss and weakness appear. The sensory deficits tend to occur in the lateral arm and forearm and first two digits. Weakness most often occurs in the deltoid, biceps, supraspinatus, infraspinatus, and serratus anterior muscles. Significant atrophy can occur in the affected muscles. The pain usually lessens within 3 to 6 weeks. Sensory loss and weakness improve over months, but long-term deficits may persist. The acquired form tends not to recur but the familial form can.

   Differentiation from a cervical nerve root compression syndrome requires cervical spine imaging. Imaging of the plexus may show signal enhancement or enlargement in the affected portions. Electrodiagnostic studies show acute denervation patterns on needle EMG in limb muscles but sparing of the parapinals. Conduction studies show low amplitude sensory nerve action potentials in amplitude in affected nerves, a finding that also helps distinguish plexopathy from radiculopathy.
2. **Treatment.** The lesion is presumably inflammatory in nature but treatment with oral or intravenous corticosteroids have shown no consistent benefit in small trials. The pain is often poorly responsive to even major analgesics but should be managed symptomatically as best as possible.

Metabolic Neuropathies

E. Alcoholic neuropathy is a sensorimotor polyneuropathy that primarily affects the distal legs but can also produce mononeuropathies.

1. **Clinical features and diagnosis.** The onset of the polyneuropathy is insidious, and progression takes place over months or longer. Sensory symptoms include numbness, paresthesia, and fiery pain. Motor abnormalities in the form of deficits of toe abduction or extension are present in many patients. Foot-drop can occur in more advanced cases. Electrodiagnostic studies show a pattern of axonal disease. Supporting laboratory findings include liver enzyme abnormalities and red cell macrocytosis.
2. Treatment consists of discontinuance of alcohol and establishment of an adequate diet plus supplementation of the diet with thiamine at 100 mg per day. Improvement takes place over months. Unstable walking resulting from concomitant alcoholic cerebellar disease recovers less well than the neuropathy and can limit overall improvement.

3. **Mononeuropathy** results from local compression of nerves during periods of alcoholic obtundation. Radial neuropathy at the humeral spiral groove causing wrist drop is the classic lesion. The deficit tends to recover over days to months as the pressure-injured internodal segments remyelinate. If deficits do not begin to improve within a month of onset, electrodiagnostic testing should be done to better define the degree of nerve injury and establish prognosis.

F. **Diabetic neuropathy** can appear in several different forms, which are not mutually exclusive. Other than optimal control of blood glucose levels there is still no specific therapy for biochemical abnormalities underlying the neuropathy. The principles of general symptom management outlined in Section I. should be followed.

1. **Sensorimotor polyneuropathy** causing bilateral foot numbness with or without a painful component is the most common type of diabetic neuropathy. Good control of blood glucose is the foundation of management, but neuropathic symptoms may develop despite this.
2. **Lumbosacral plexopathy,** also termed diabetic amyotrophy or radiculoplexopathy, is a distinctive syndrome (see Chapter 25, II.A.). The condition usually begins with spontaneous unilateral pain in the low back, hip, or proximal leg. The pain can become quite severe over the next week or so. Days or, more often, a few weeks after onset of the pain, paresthesia and sensory loss appear in the thigh and at times in the medial lower leg. Weakness most often affects the quadriceps and appears about the same time as the sensory loss. Notable muscle atrophy can occur in the affected muscles. The pain is often only partially responsive to even major analgesics but tends to begin improving within a month or 2 after onset. Considerable weight loss may occur with this condition. Occasionally, as the initially involved side is improving, the opposite side becomes involved. The long-term prognosis tends to be good, but recovery can extend over a year or more. Some patients have persisting motor deficits. Several small series in the literature suggest that a course of intravenous gamma globulin or corticosteroids by the oral or intravenous route may shorten the course of this syndrome. The dosing schemes outlined for the initial treatment of chronic inflammatory neuropathy can be utilized. Steroid dosing has not been standardized.
3. **Thoracic radiculopathy** is somewhat similar to lumbosacral plexopathy in terms of onset and time course. Unilateral band-like pain beginning spontaneously in the chest or upper lumbar region is the main symptom. The pain can be severe. Cutaneous hypersensitivity that makes the touch of clothing uncomfortable in the involved area also may be reported. Localized weakness of the lateral or anterior abdominal muscles may produce localized bulging of the abdominal wall, particularly when the patient is standing. Analgesics provide at best partial relief. Gabapentin and tricyclic antidepressants may partially improve the pain. Local anesthetic nerve blocks or topical lidocaine patches in the involved dermatome may help to some degree, as can use of a transcutaneous electrical nerve stimulation unit. The pain persists for some months but eventually resolves or greatly improves.

Medication Induced Neuropathies

G. Medication induced polyneuropathy can occur during treatment for neoplasms, autoimmune disorders, chronic infrections, and cardiac arrhythmia. Vincristine, paclitaxel and docetaxel, cis and carboplatinum, and bortezemab are the antineoplastic drugs most often associated with neuropathy. Colchicine, hydroxychloroquine, leflunomide, and thalidomine used for treatment of inflammatory and autoimmune disorders can cause neuropathy. The antibiotics dapsone, isoniazid, metronidazole, and nitrofurantoin have been reported to cause neuropathy. The antiarrythmic medication amiodarone can cause neuropathy.

1. **Clinical features.** All of these except platinum produce a sensorimotor neuropathy and the sensory deficits are usually the prominent features. The platinum compounds tend to affect only sensory neurons and can produce both sensory loss and ataxia. A significant painful component may develop with some of these agents. Motor deficits are usually mild, but if sensory deficits progress proximally to the mid-shin and fingertip levels,

foot drop and weakness of the intrinsic hand muscles can occur. The occurrence and severity of neuropathy tend to be dose related and usually begin after several cycles of administration. The patients are actively aware of the deficits. Nerve conduction studies can help quantify the deficits.

2. **Treatment.** When repeated or prolonged use of the medication is required for treatment of the primary illness, lengthening of the interval between treatment or reduction of the dose at each treatment may allow the neuropathy to stabilize. Improvement is the expected course but the time interval may extend over months or longer. Some patients worsen for weeks to a few months after the dosing is reduced or stopped. The clinical pattern is termed "coasting." Symptoms should be managed as described above in Section I.

Neuropathies Due to Infections

H. Lyme's disease can produce several different types of peripheral neuropathy as well as other neurological manifestations such as meningitis and a delayed chronic encephalopathy. The bites of certain ticks of the *Ixodes* genus (e.g., *I. dammini*, most often) transmit the infectious agent *Borrelia burgdorferi*. Endemic areas include southern New England and the Mid-Atlantic states, the central regions of Wisconsin and neighboring states, and north coastal California plus Oregon.

1. **Clinical features.** The characteristic skin lesion erythema chronic migraines develops 3 to 20 days after the bite, as does a general flu-like syndrome of fever, malaise, and myalgia. The skin lesion occurs in approximately 80% of cases. Frank neurologic involvement occurs in approximately 15% of cases and tends to appear 1 to 3 months after the initial infection in the time frame termed the *early disseminated phase* of the illness. Less specific symptoms of headache occur in more than half of patients. A positive serologic result for antibodies against the infectious agent is helpful for establishing the cause, but test results may be negative for a month or so after the initial infection. An ELISA or immunofluorescence assay should be done first and if positive be followed up by an immunoblot test for IgM or IgG antibodies. The latter test helps to identify false-positive results.
2. **Treatment.** Antibiotic treatment appears to relieve all of the manifestations, either by shortening the duration of episodes or by alleviating more persistent symptoms such as polyneuropathy. Oral antibiotics can be used to manage the rash and flu-like phase of the initial stage of the infection. For adults, doxycycline 100 mg twice a day, amoxicillin 500 mg three times a day, or cefuroxime 500 mg twice a day for 2 to 3 weeks are recommended. Peripheral and central nervous system manifestations are best managed with intravenous penicillin G, 20 million U per day, or ceftriaxone, 2 g daily for the same 2 to 3 weeks.
3. **Types of neuropathy of the early disseminated phase.**
   a. **Facial nerve involvement** produces typical Bell palsy, including pain in the ear region. Bilateral involvement occurs more frequently with Lyme's disease than in the idiopathic form.
   b. **Radiculitis** producing a syndrome similar to that described for diabetic thoracic radiculopathy (see II.E.3.) and consisting of dermatomal pain, which can reach a high level of intensity, sensory loss, and focal weakness. Limb as well as truncal spinal segments can be involved.

I. HIV infection can be associated with several types of peripheral neuropathy.

1. Typical **acute inflammatory demyelinating neuropathy,** Guillain–Barré syndrome, can occur early in the course of the infection. CSF pleocytosis with white cell counts of 10 or more is the only feature that distinguishes this form from the idiopathic variety. Therapy should be the same as for the idiopathic form of the disorder (see II.A.3.).
2. A **distal symmetrical polyneuropathy** with predominant painful symptoms can also occur in up to a third of patients and is more likely when viral load becomes greater than 10,000 copies per ml. Patients report painful paresthesia consisting of pressure- or burning-type sensations in the feet and distal legs. The hands can be involved to a lesser extent. Weakness is minimal. CSF tends to be normal to minimally abnormal.

Nerve conduction studies show a pattern of axonal damage. Management of this type of neuropathy is symptomatic only, and the general guidelines for painful neuropathy presented in I.A. should be followed. A similar type neuropathy can occur in patients being actively treated with high activity antiretroviral therapy (HAART). This type neuropathy has symptoms and signs very similar to those produced by the HIV infection. A potential clue that the neuropathy is treatment-related is its appearance after HAART has been begun. Dosage reduction or substitution of potentially less neurotoxic medications should be considered if the status of the infection permits.

3. **Polyradiculitis** resulting from infection by **cytomegalovirus** is another distinctive form of neuropathy that affects patients with AIDS in the advanced stage of the illness. Patients report pain and weakness in the lower extremities and the back. The onset may be asymmetrical but becomes bilateral within days to weeks. Sensory loss develops in the limbs and perineal area. Bladder and bowel incontinence are also regular features. Progression to arm involvement is infrequent. CSF shows pleocytosis and elevated protein level. Pathologic specimens show inflammation of the nerve roots of the lumbar and sacral areas. **Treatment** with ganciclovir and foscarnet may stabilize the condition, but this lesion tends to be a poor prognostic indicator.

Other Neuropathies

J. Critical illness polyneuropathy occurs in patients who experience severe episodes of sepsis and multi-organ failure that require days to weeks of treatment in the intensive care unit.

1. **Clinical features.** The neuropathy typically becomes evident when respiratory support is withdrawn and the patient remains severely weak. Sensory loss may be found in patients with sensoriums clear enough for a detailed neurologic examination. Guillain–Barré syndrome is often considered in this setting. The CSF protein level tends to be normal in critical illness polyneuropathy in contrast to the latter. Nerve conduction studies show axonal rather than demyelinating patterns. Critical illness myopathy can also occur in this same setting. This condition is distinguished from the neuropathy by the finding of normal sensory examination and normal sensory nerve conduction studies. The myopathy patients have often received high-dose corticosteroids and nondepolarizing neuromuscular blocking agents as part of the ventilator support during the critical illness.
2. **Treatment.** Management is supportive. Recovery occurs over months. Aggressive management of hyperglycemia, which can occur in the acute phase of the critical illness, appears to lessen the occurrence of this neuropathy.

Recommended Readings

Amato AA, Russell JA. *Neuromuscular Disorders*. New York, NY: McGraw Hill Medical; 2008.

Bromberg MB, Smith AG, eds. *Handbook of Peripheral Neuropathy*. Boca Raton, FL: Informa Healthcare; 2005.

Dyck PJ, Thomas PK, eds. *Peripheral Neuropathy*. 4th ed. Philadelphia, PA: Saunders; 2005.

McKahnn GM. Guillain-Barré syndrome: clinical and therapeutic observations. *Ann Neurol*. 1990;27(suppl):S13–S16.

Van Doorn PA, Vermeulen M, Brand A, et al. Intravenous gamma globulin in treatment of patients with chronic inflammatory demyelinating polyneuropathy. *Arch Neurol*. 1991;48:217–220.

CHAPTER

47 Myopathy

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Myopathy is an abnormality of the skeletal muscle in which striated muscle cells or connective tissue elements are affected. Myopathy can result from abnormalities of skeletal muscle proteins (Duchenne muscular dystrophy), alterations of the sarcolemmal ion channels (hyperkalemic periodic paralysis), mitochondrial alterations (mitochondrial myopathy), or cell-mediated autoimmune mechanisms (polymyositis), to name a few examples. Because of the myriad abnormal mechanisms, treatments vary from one condition to the next. Progress in molecular biology, genetics, and immunology has considerably expanded our understanding of these complicated diseases. This chapter emphasizes current therapeutic approaches to the care of patients with relatively common forms of myopathy.

I. IDIOPATHIC INFLAMMATORY MYOPATHY

Idiopathic inflammatory myopathies are autoimmune diseases characterized by muscle weakness, pain, and fatigue. Inflammatory damage of muscle fibers is the underlying pathology. **Polymyositis** can occur in isolation or accompany other connective tissue disorders or associated systemic autoimmune disorders. **Dermatomyositis, inclusion body myositis (IBM),** and **polymyalgia rheumatica (PMR)** are the other major categories of idiopathic inflammatory myopathy. The incidence of these diseases is approximately 1 case among 100,000 persons.

A. Natural history and prognosis.

1. **Polymyositis** usually affects upper and lower girdle muscles in a symmetric pattern after the second decade of life. Patients with no family history of muscle weakness have subacute (weeks to months), progressive weakness of the deltoid, trapezius, neck flexor and extensor, biceps, triceps, iliopsoas, gluteus, quadriceps, and other muscles.

   Patients characteristically have problems arising from a sitting position, washing their hair, or using stairs. Muscle pain may accompany the weakness. Pharyngeal muscle compromise can lead to dysphagia. The tongue, extraocular muscles, and facial muscles are usually spared. Sensation is not affected. Cardiac involvement can occur in as many as 40% of cases. Pulmonary involvement can result from primary weakness of respiratory muscles or from pulmonary interstitial fibrosis.

   Polymyositis can occur in association with connective tissue and systemic autoimmune disorders. Polymyositis is not associated with an increased incidence of malignant disease. T-cell-mediated immunity plays a prominent role in the pathogenesis of polymyositis.
2. **Dermatomyositis** is characterized by a rash that accompanies or precedes muscle weakness. The characteristic skin abnormality is a heliotrope rash over the orbits and zygomatic arch with erythema on the rest of the face, upper trunk, and knuckles (Gottren's papules). Subcutaneous nodular calcifications and dilated capillaries in the nail beds occur.

   In children, extramuscular manifestations are more frequent than they are in adults. Dermatomyositis usually occurs alone but may be associated with systemic sclerosis, mixed connective tissue disease, or malignant lesions. Ten percent of patients with dermatomyositis will be found to have an underlying malignancy. It is a humorally mediated microangiopathic disorder with vascular deposition of immunoglobulin G (IgG), C3, and membrane attack complex. This suggests that the primary immunologic event is generation of antibodies against antigens within the walls of intramuscular blood vessels.
3. **IBM** involves distal and proximal muscles. Weakness and atrophy can be slightly asymmetric; quadriceps and finger flexors are commonly affected. It is a late-onset myopathy (sixth or seventh decade). It is treatment resistant. Occasionally, the diagnosis of IBM

is made retrospectively when a patient fails to respond to treatment for polymyositis. Hereditary forms of IBM have been described: an autosomal dominant variant, which has a younger age of onset and an autosomal recessive variant, caused by a mutation in the GNE gene, on chromosome 9.

4. **PMR** affects elderly men and women with a peak incidence at 74 years of age. Patients describe diffuse muscle aching with neck and shoulder stiffness. Pain predominates over weakness or atrophy. Approximately 15% of the patients also have temporal arteritis. The erythrocyte sedimentation rate (ESR) is elevated to >40 mm per hour.
5. Noninfectious inflammatory myositis can also occur in the context of systemic lupus erythematosus, progressive systemic sclerosis, Sjögren's syndrome, rheumatoid arthritis, mixed connective tissue disease, sarcoidosis, hypereosinophilic syndromes, and other disorders.

B. Diagnosis. In addition to the clinical features, the diagnosis of inflammatory myopathy is supported by results of measurement of muscle enzymes, electromyography (EMG), and muscle biopsy.

1. **Muscle enzymes.** Creatine kinase (CK) is released from the sarcoplasm into the serum after muscle destruction, and the level may be elevated as much as 50-fold in polymyositis/dermatomyositis. Other muscle enzymes such as lactate dehydrogenase, aldolase, and aminotransferases are commonly elevated. In IBM, CK level may be elevated as much as 10-fold or remain normal. In childhood dermatomyositis and in patients with myopathy associated with connective tissue diseases, CK levels may be normal. ESR should be determined, especially for suspected PMR.
2. The main value of **EMG** resides in its ability to show that peripheral neuromuscular weakness originates from the muscle itself and not from denervation or from a defect in neuromuscular transmission. It can also help ascertain the presence of disease activity. The classic EMG findings include short-duration, small-amplitude motor unit potentials, and increased insertional activity. These findings should not be considered specific for inflammatory myopathy, because they can also be found in acute toxic or metabolic myopathy and in dystrophy.
3. **Muscle biopsy** helps establish the diagnosis.
   a. In **polymyositis,** light microscopic examination displays intrafascicular inflammatory infiltrates, necrosis, atrophy and regeneration of muscle fibers, and increased amounts of connective tissue.
   b. In **dermatomyositis,** the inflammatory infiltrates are present around the vessels or in the interfascicular septa, and perifascicular atrophy is characteristic. Small blood vessels with hyperplastic endothelia may be occluded.
   c. **IBM** is characterized by basophilic granular inclusions around the edges of vacuoles (rimmed vacuoles).
   d. Muscle biopsy has **limitations.** Because of sampling error, a biopsy sometimes fails to disclose abnormalities expected from the clinical presentation.

C. Therapy.

1. **Prednisone.**
   a. **Administration.** High-dose prednisone is the initial line of therapy for polymyositis and dermatomyositis. For prednisone, the recommended dosage is 1.0 mg per kg a day in a single daily dose for 30 to 60 days. The total dose should not exceed 100 mg. Daily administration should be used until there is unquestionable improvement muscle strength with recovery of ambulation. Then the dosage can be slowly reduced over 10 weeks to 1 mg per kg every other day. If no deterioration occurs, the dose is further reduced by 5 to 10 mg every 3 to 4 weeks until the lowest dose that controls the disease is reached. The dose should not be reduced if strength decreases. If treatment is effective, strength should improve within 3 months. If after 3 months of therapy no improvement has been achieved, prednisone should be tapered off and another immunosuppressant medication begun.
   b. **Side effects.** Patients need to become acquainted with the numerous side effects of long-term prednisone treatment. Infections, fluid retention, potassium depletion, hypertension, diabetes, osteoporosis, premature cataracts, peptic ulcer disease, and skin bruising are some of the side effects that can occur.

Prevention of osteoporosis requires supplemental calcium gluconate or carbonate (500 to 1,000 mg per day) and calcitriol (0.2 to 0.5 mg per day) as well as axial exercise and adequate passive range of motion maneuvers. Bisphosphonates (alendronate, risedronate among others) can be used. A baseline dual energy X-ray absorption densitometry scan to measure bone density should be obtained for every patient before steroid treatment is started. The scan should be repeated every 6 months.

Proton pump inhibitors should be used to prevent peptic ulcers. Periodic eye examinations are needed for diagnosis of incipient cataracts or glaucoma. Periodic laboratory tests for serum glucose and electrolytes are recommended. Steroid myopathy, a side effect of long-term steroid use, will be addressed later in this chapter.

2. Sometimes patients with dermatomyositis need separate therapy for the rash.
3. **Azathioprine** is considered when complications preclude use of steroids, when the disease is not responding to adequate dosages of prednisone, or to add a steroid-sparing agent. A therapeutic response may take 3 to 6 months.
   a. **Administration.** Azathioprine can be administered at 2 (up to 3) mg per kg a day. The initial dose should be approximately 50 mg per day, gradually increasing to BID dosing.
   b. **Side effects.** The most common side effects of azathioprine are fever, nausea, rash. However, bone marrow suppression and liver toxicity can occur. CBC count with differential and platelets and liver function tests should be performed weekly for the first month and monthly thereafter. Patients with absent thiopurine S-methyltransferase (TPMT) enzyme activity are at high risk for azathioprine toxicity. TPMT testing is commercially available and may be considered before beginning treatment with azathioprine.
4. **Mycophenylate mofetil** inhibits proliferation of T and B lymphocytes and can be used as an alternative to azathioprine. Doses typically start at 500 mg per day and are increased to 1,000 mg twice a day. Side effects include immunosuppression, gastrointestinal side effects, hepatotoxicity and bone marrow inhibition, possible reactivation of chronic infection such as tuberculosis, and remote risk of malignant disease.
5. **Methotrexate** (15 to 25 mg per week by mouth) is used as another method to spare use of prednisone or if prednisone has not been effective. Hepatotoxicity, leukopenia, alopecia, stomatitis, and risk of neoplasia can occur. Methotrexate should not be used in patients with anti-Jo-1 antibodies and polymyositis because they are at increased risk for pulmonary fibrosis.
6. **High-dose intravenous (IV) gamma globulin** is effective in the management of polymyositis and in dermatomyositis. The recommended dosage is 0.5 mg per kg IV for 4 days, repeating each month as needed. Side effects include headaches, hypertension, acute renal failure, and hyperviscosity. Aseptic meningitis can occur and may respond to prednisone treatment. IgA-depleted preparations reduce the risk of reactions related to anti-IgA antibodies. Treatments are expensive. Despite these reservations, high-dosage IV gamma globulin might benefit patients who have been unresponsive to other medications.
7. In refractory cases, or if interstitial lung disease occurs, **cyclophosphamide** (1 to 2 g per m^2 a month IV) may be considered. Side effects include nausea, vomiting, alopecia, hemorrhagic cystitis, teratogenicity, bone marrow suppression, carcinogenesis, and pulmonary fibrosis. Cyclophosphamide can also be used orally at doses of 1 to 2 mg per kg a day.
8. **Rituximab,** a CD20 monoclonal antibody that depletes B cells, is being investigated for use in resistant disease. It is administered at a dose of 375 mg per m^2 every week for a month, with possible repeat courses in 6 months or 1 year. Opportunistic infections have occurred with this medication.
9. In **PMR,** prednisone rapidly provides benefits. Duration of treatment and dosage have to be individualized. In general, a starting dosage of 1 mg per kg a day should be appropriate. In patients suffering from temporal arteritis, corticosteroid treatment needs to be initiated immediately.

D. **Prognosis.** Dermatomyositis and, to a lesser degree, polymyositis are responsive to treatment, whereas IBM is usually resistant. Patients with interstitial lung disease have a higher mortality rate. When management of polymyositis is unsuccessful, the patient should be reevaluated and the muscle biopsy specimen reexamined to exclude

IBM or muscular dystrophy of the limb-girdle type. Finally, it is important to emphasize the need to evaluate the patient's strength and activities of daily living as measures of improvement, rather than simply adjusting treatment on the basis of CK levels alone.

II. VIRAL INFLAMMATORY MYOPATHY

Viruses and retroviruses can cause acute or subacute inflammatory myopathy.

A. Reye's syndrome is acute encephalopathy with fatty degeneration of the liver that develops after varicella or influenza infections. This rare condition that affects children and adolescents begins with repeated vomiting and continues with confusion, lethargy, and coma. The mortality is high. There is acute liver dysfunction. The level of CK MM isoenzyme derived from skeletal muscle may be increased 300-fold. The level of CK correlates with prognosis. Salicylates may precipitate the syndrome. Treatment is supportive. The incidence of this syndrome has decreased precipitously over the years because aspirin is no longer being used to treat children with flu-like symptoms.

B. HIV may cause subacute or chronic myopathy early or late in relation to the infection. Proximal, symmetric involvement of lower or upper limbs manifests as weakness with or without atrophy. Serum CK levels may be elevated 10 to 15 times. The syndrome is almost identical to polymyositis. Thus, in the evaluation of patients with polymyositis, evaluation for HIV is recommended.

III. PARASITIC INFLAMMATORY MYOPATHY

In North America, **trichinosis, cysticercosis,** and **toxoplasmosis** are rarely the cause of a myopathy. These causes may need to be considered in an acute–subacute onset myopathy in an immunocompromised patient or one who has been in an endemic area or has had possible exposure to the parasite.

IV. PERIODIC PARALYSES

Periodic paralyses are disorders characterized by episodes of flaccid muscle weakness that can evolve into paralysis. Attacks usually last hours. Periodic paralysis is either a primary autosomal dominant disorder or a secondary disorder. The inherited forms of these diseases are caused by **channelopathies,** or defects in genes coding for muscle membrane ion channels (Table 47.1).

A. Natural history and prognosis.

1. **Primary hypokalemic periodic paralysis** affects young and middle-aged persons. Attacks usually occur at night or after strenuous exercise. On awakening, patients may be paralyzed and unable to get out of bed. The flaccid paralysis usually spares the respiratory and cranial muscles. During attacks, serum potassium level decreases. An ECG may reveal hypokalemic changes, including progressive flattening of T waves, depression of the ST segment, and appearance of U waves. Some patients eventually develop a progressive myopathy.

   Seventy percent of patients with this disorder have a defect in the calcium channel gene: CACNA1S, which is located on chromosome 1q31. A small percentage of patients, however, have a sodium channel defect (SCN 4A). For approximately 20% of patients the gene defect is yet to be identified.

2. **Secondary hypokalemic periodic paralysis.**
   a. **Thyrotoxic periodic paralysis** occurs 70 times more often in men than in women, despite the increased prevalence of hyperthyroidism among women. In nearly all cases, the condition is sporadic and the attacks cease when thyroid function is normalized. Every patient with hypokalemic periodic paralysis needs screening for thyrotoxicosis. This condition is more common in patients of Asian, Hispanic American, and Amerind origin.

TABLE 47.1 Channelopathies

Channel	hypoK+ PP	hyperK+ PP	Andersen–Tawil	Paramyotonia Congenita	Myotonia Congenita
SCN4A	+	+		+	
CLCN1					+
CACNA1S	+				
KCNJ2			+		
Myotonia on EMG		+/−		+	+
Acetazolamide responsive	+	+	+/−		

Abbreviations: hypoK+ PP, hypokalemic periodic paralysis; hyperK+ PP, hyperkalemic periodic paralysis.

b. **Periodic paralysis secondary** to urinary or gastrointestinal potassium loss can result from primary hyperaldosteronism, excessive thiazide therapy, excessive mineralocorticoid therapy for Addison's disease, renal tubular acidosis, the recovery phase of diabetic coma, sprue, laxative abuse, villous adenoma of the rectum, or prolonged gastrointestinal intubation or vomiting.

3. **Hyperkalemic periodic paralysis** produces episodic attacks of weakness accompanied by elevations in serum potassium level (up to 5 to 6 mmol per L). It can be associated with myotonia (inability to relax the muscle) or paramyotonia (muscle stiffness worsened by exercise or cold). It is inherited in an autosomal dominant manner. Attacks start in the first decade of life. Patients usually have brief periods of generalized weakness. Static weakness is rare. Sustained mild exercise may prevent attacks. Cardiac arrhythmias can occur.
   a. The **genetic abnormality** is a mutation in the SCN 4A (sodium channel) gene.
   b. **Needle EMG** may detect myotonia, which supports the diagnosis.
4. **Andersen's syndrome (or Andersen–Tawil's syndrome)** is a triad of facial dysmorphism, long QT syndrome, and periodic paralysis. Short stature is often also present. Andersen syndrome is an autosomal dominantly inherited disease with a young age of onset and phenotypic variability. Fatal cardiac dysrhythmias may occur, making early recognition of this condition important. Mutations in the KCNJ2 gene, which codes for an inward-rectifying potassium channel, have been found in some patients.
5. **Chloride channel mutations** produce **myotonia congenita** with dominant and recessive forms (Thomsen and Becker, respectively), and with more myotonia than weakness. The dominant form manifests as painless muscle stiffness. Muscle stiffness is relieved after repeated exercise (warm-up), but it returns after rest. Cooling does not produce a significant change. These disorders result from missense mutations in the chloride channel gene CLCN1.

B. Prevention and therapeutic approach.

1. **Primary hypokalemic periodic paralysis.** Mild attacks may not require treatment. For attacks of general paralysis, oral potassium chloride can be used (0.25 mEq per kg), repeated every 30 minutes until the weakness is relieved. Muscle strength usually recovers within approximately 1 hour. IV potassium is not recommended because of the danger of cardiac arrhythmias and should be avoided.

   For **prevention** of attacks, acetazolamide is the drug of choice, starting at 125 mg every other day, which can be increased to 250 mg three times a day. Side effects include increased incidence of nephrolithiasis, paresthesia, anorexia, and metallic taste. In severe cases, patients should eat a low-salt diet and be given the aldosterone antagonist spironolactone (100 mg twice a day) or triamterene (150 mg per day). Both drugs promote renal potassium retention.
2. **Thyrotoxic periodic paralysis.** Return to euthyroid status is curative. Propranolol (40 mg four times a day) and other β-adrenergic blocking agents may prevent attacks, possibly by suppressing the adrenergic overactivity induced by hyperthyroidism.

3. **Hyperkalemic periodic paralysis.**
   a. **Preventive measures** consist of low-potassium diet, avoidance of fasting, and avoiding strenuous exercise. Slight exercise or ingestion of carbohydrates at the onset of weakness may prevent or abort attacks.
   b. A thiazide diuretic, acetazolamide, or inhalation of a β-adrenergic agent (metaproterenol or salbutamol) may **abort an attack.** Dilantin (300 mg per day) can also be useful. For **long-term preventive therapy,** a thiazide diuretic or acetazolamide is recommended at the lowest possible dosage (hydrochlorothiazide, 25 mg every other day).
4. In **myotonia congenita,** mexiletine has been used. The starting dose is 150 mg by mouth twice a day, up to 1,200 mg per day. Mexiletine is contraindicated in the case of patients with second- and third-degree heart block; other cardiac arrhythmias can occur.

V. MUSCULAR DYSTROPHY

Muscular dystrophy is the term for inherited defects of cellular muscle structure, producing intrinsic muscle weakness. Some forms present at childbirth, others as late as the seventh decade. Family history, clinical examination, and temporal profile are necessary when considering a muscular dystrophy. The number of inherited dystrophies and the enormous variety of phenotypes prevent complete coverage in this forum. The following dystrophies will be discussed: **X-linked dystrophinopathy** (**Duchenne** and **Becker muscular dystrophy), facioscapulohumeral dystrophy, myotonic, limb-girdle,** and **oculopharyngeal.**

A. Natural history and prognosis.

1. **Dystrophinopathy** is an X-linked disorder caused by a mutation in the short arm, locus 21, of the X chromosome in the enormous gene that codes for the protein dystrophin. Dystrophin is a filamentous protein present in striated and cardiac muscle and other tissues. Although the role of dystrophin is not precisely known, anchoring and structural functions have been proposed for this protein.

   In the most severe form of dystrophinopathy—Duchenne muscular dystrophy—almost no dystrophin is detected in skeletal muscle. In milder allelic forms—phenotypically denominated as Becker muscular dystrophy—some muscle fibers express dystrophin, which may be structurally abnormal. Almost all patients with dystrophinopathy are male. The disease can be caused by spontaneous mutations, which are more common than in other genetic disorders, probably because of the large size of the gene. Approximately 70% of patients with Duchenne and Becker muscular dystrophy have detectable mutations on routine DNA testing of peripheral blood. Deletions of varying sizes can be found in approximately 65% of cases; 5% of patients have gene duplications. A negative result of a DNA test does not exclude the diagnosis because approximately 30% of patients have an undetected mutation. The diagnosis in these patients depends on dystrophin analysis at muscle biopsy.

   a. **Duchenne muscular dystrophy** affects children early in life. Motor developmental delay is noticeable after the first year, but muscle necrosis and serum enzyme elevation can be found in neonates. Onset of walking may be delayed past 15 months of age. Signs are present before the age of 5 years. They include difficulties in running and climbing stairs.

      Children have hyperlordosis with prominent abdomen and calf pseudohypertrophy. Tiptoe walking is common. To stand up from the floor, patients use their hands (**Gower's sign**). Joint contractures of the iliotibial bands, hip flexors, and heel cords develop in most patients by 6 to 9 years of age. By the age of 10 years, many of these patients lose the ability to walk or stand and must use a wheelchair. By the midteens they lose upper-extremity function. Cognitive dysfunction occurs in 10% of cases. The disease is usually fatal by the end of the second decade. Death is usually related to pulmonary infection, respiratory failure, or cardiomyopathy. Approximately 8% of female carriers have myopathy of the limb-girdle type. Female carriers may also have isolated cardiomyopathy.

      Muscle biopsy specimens from patients with Duchenne muscular dystrophy have abnormal variations in fiber size, fiber splitting, central nuclei, and replacement by fat and fibrous tissues. The diagnosis of Duchenne's muscular dystrophy can be confirmed by an **absence of dystrophin immunostaining.**

An EMG obtained early in the course of the disease shows findings compatible with those of myopathy. In end stage, there are decreased numbers of muscle fibers and the tissue can even become inexcitable.

b. **Becker's muscular dystrophy** is a milder variety of dystrophinopathy in terms of severity and molecular abnormality. The diagnosis has been variably defined as either a patient who remains ambulatory or who has symptom onset after age 12. Patients may live many decades with mild to moderate symptoms, which can be indistinguishable from those of limb-girdle dystrophy. Patients are at risk for cardiomyopathy.

2. **Facioscapulohumeral muscular dystrophy** is an autosomal dominant disease that has high penetrance. It affects both men and women and starts before 30 years of age. Ninety-five percent of patients have a deletion in a sequence of a 3.3-kilobase repetitive unit (known at D4Z4) in chromosome 4q35.

   Clinically, facial muscles are affected early. Bell's phenomenon (failure of eyelids to close completely when the patient is sleeping or blinking) and drooping of the lower lip are noticeable. Patients may be unable to whistle. Facioscapulohumeral muscular dystrophy also involves the trapezius, rhomboid, and serratus anterior scapular muscles. Scapular winging is noticed with forward arm movement because of serratus anterior weakness. Deltoid function and rotator cuff muscles are better preserved. Patients typically seek medical attention because of the involvement of the shoulder rather than of the facial muscles. Lower-extremity weakness is found later in the disease.

   This disorder has wide phenotypic variability, even within the same family. Some patients remain ambulatory all their lives, whereas others progress to using a wheelchair. The heart is usually spared. Trunk weakness may also occur.

3. **Oculopharyngeal muscular dystrophy** is an autosomal dominant disease of late onset. This syndrome manifests as ptosis and progressive dysphagia. Muscle biopsy shows rimmed vacuoles in muscle biopsy specimens, and tubulofilamentous inclusions within the striated muscle cell nucleus. The differential diagnosis includes myasthenia gravis and mitochondrial myopathies (Kearns–Sayre's syndrome).

4. **Limb-girdle muscular dystrophy** is a heterogeneous collection of both autosomal recessive and autosomal dominant disorders that affect pelvic and upper girdle muscles and spare the face. Some disorders present in childhood, others into late adulthood.

5. **Myotonic dystrophy** is the most common muscular dystrophy among adults. Rather than being restricted to the skeletal muscle, it is a multisystemic, autosomal dominant disorder. It also involves the pancreas, gonads, thyroid, myocardium, and brain. Myotonic dystrophy is produced by a trinucleotide repeat expansion in chromosome 19 (19q13.2–13.3) that codes for myotonin protein kinase, a ubiquitous enzyme related to protein phosphorylation. The molecular gene defect consists of a CTG repeat expansion (>80) within the gene and the length of the repeat is correlated with the severity of the disease and inversely correlated with symptom onset. Clinical diagnosis is supported by the presence of myotonic discharges on EMG.

   a. **Muscle features.** Weakness of facial muscles is typical. The face is hatched and thin with early frontal balding. Ptosis is present but is not as severe as in myasthenia gravis or Kearns–Sayre's syndrome. Temporalis and masseter atrophy is a characteristic feature. Limb involvement is predominantly distal. Proximal limb muscles are usually preserved until the late stages. Myotonia, which is the delay of muscle relaxation after contraction, is present. Myotonia can be elicited by percussion of the thenar eminence or tongue. Patients may be unable to release their grip after a handshake.

   b. **Generalized features.** Many patients have prominent systemic symptoms. Common abnormalities include cataracts, testicular atrophy, adult-onset diabetes mellitus, thyroid dysfunction, heart block, and arrhythmias. Hypersomnia and excessive daytime somnolence are reported and patients are often found to have mixed obstructive and central apneas. Because of the cardiorespiratory compromise, patients are susceptible to complications during surgery and anesthesia. Cognitive dysfunction, apathy, and lethargy are seen in more severely affected patients.

6. **Myotonic dystrophy type 2 or proximal myotonic myopathy** is an autosomal dominant disorder characterized by progressive weakness, myotonia, and cataracts. This is caused by a tetranucleotide repeat (CCTG) in the zinc finger protein 9 gene (ZNF9).

These patients are a phenotypically milder form of myotonic dystrophy, with a later onset of symptoms.

7. **Mitochondrial myopathies** are a category of inherited diseases in which the genetic defect is either in the mitochondrial DNA or in a nuclear DNA gene that encodes for a protein involved in the mitochondrial respiratory chain. Because these defects all produce mitochondrial dysfunction, leading to decreased cellular energy production, patients manifest with symptoms related to oxidative stress. Seizures, encephalopathy, strokes, cardiomyopathy, muscle weakness (especially extraocular muscles), short stature, and hearing loss are common symptoms. The genetics underlying mitochondrial myopathies are complex. Mitochondrial DNA defects are maternally inherited and heteroplasmy (unequal distribution of affected mitochondria) may occur. Nuclear DNA genetic abnormalities follow Mendelian genetics.

   Measurement of function of the components of the respiratory chain, muscle biopsy, MRI of affected organs, pedigree analysis, and genetic analysis of the mitochondrial genome can assist in making the diagnosis. Some of the more common phenotypes are mitochondrial encephalopathy with ragged red fibers, mitochondrial encephalopathy with lactic acidosis and stroke-like syndrome, chronic progressive external ophthalmoplegia, Kearns–Sayre's syndrome, and Leigh's disease.

B. Therapeutic approach.

1. **Duchenne muscular dystrophy.**
   a. **Family and patient education** is important. A multidisciplinary clinic which specializes in muscular dystrophy can provide specialists and support to the patient and families.

      Genetic counseling is recommended. Mothers and female siblings can be assessed for carrier status by assessment of serum CK or, if the patient has a documented genetic defect, through peripheral blood genetic analysis. However, negative results of mutation analysis in the mother do not rule out the risk of Duchenne muscular dystrophy affecting future pregnancies. Even with normal results of peripheral blood gene analysis, a mutation can be present in a percentage of oocytes (germline mosaicism).

   b. **Physical therapy** is used to preserve mobility and to prevent early contractures. Passive range of motion exercises and adequate orthotics may prolong ambulation but do not stop disease progression.

      Orthotics and splints can assist with managing contractures. All patients progress to wheelchair dependency: proper wheelchair assessments and fittings can lessen the development of scoliosis.

      Patients with Duchenne muscular dystrophy are at high risk of side effects of general anesthesia. Succinylcholine or halothane should not be used because of the risk of episodes that resemble malignant hyperthermia. Adverse effects can be reduced with the use of nondepolarizing muscle relaxants.

   c. **Respiratory therapy.** In later stages, noninvasive intermittent positive-pressure ventilation is useful, especially when patients retain carbon dioxide. Pulmonary exercises, use of a cough assist device and use of a respiratory vest may prevent pulmonary infections.

   d. **Medications.** Prednisone (0.75 mg per kg a day) is recommended when children are still ambulatory to prolong this phase of life. Prednisone can improve neuromuscular strength after 1 month of treatment. The maximum effect is reached by 3 months. Side effects need to be addressed and close monitoring is needed.

   e. Therapy for **Becker muscular dystrophy** follows principles similar to those of therapy for Duchenne disease, tailored to each patient's level of strength.

2. In **facioscapulohumeral muscular dystrophy and limb-girdle muscular dystrophy,** treatment varies with individual patients. In patients with minimal symptoms, screening for cardiomyopathy and genetic counseling may be all that is needed. For patients with a foot-drop, ankle-foot orthoses may be prescribed. Physical therapy will be useful for range of motion, stretching, and gait assessment. When ambulation is impaired, a mobility evaluation can assess for wheelchair or motorized scooter needs.

3. In **oculopharyngeal muscular dystrophy,** blepharoplasty with resection of the levator palpebrae muscles may be needed. Dysphagia may be relieved with cricopharyngeal myotomy.

4. In **myotonic dystrophy,** only when myotonia is disabling, phenytoin (100 mg by mouth three times a day) can alleviate myotonia. In general, patients with myotonic dystrophy are not greatly concerned about the myotonia. The main goals are prevention and management of the systemic disease, especially cardiac arrhythmias.
5. Treatment of **mitochondrial myopathies** depends upon which organ systems are involved. Avoiding oxidative stress (hypoxia, ischemia, hypoglycemia and infection) may help prevent exacerbations or worsening. A "mitochondrial cocktail" of antioxidants and vitamins has been developed to promote respiratory chain function and includes coenzyme Q10, riboflavin, creatine, carnitine, B complex vitamins, and vitamins E and C.

VI. METABOLIC MYOPATHY

Metabolic myopathies comprise a group of inherited disorders in which the defect is an alteration in the processing of carbohydrates or fats. **Acid maltase deficiency, McArdle's disease,** and **carnitine-O-palmitoyltransferase (CPT II) deficiency** are reviewed (Table 47.2).

A. Natural history, prognosis, and treatment.

1. **Acid maltase deficiency** is an autosomal recessive glycogen storage disease caused by a deficiency in lysosomal α-glucosidase, which normally participates in the metabolism of glycogen into glucose. The infantile form is called Pompe disease; there is also a juvenile and adult onset form of this deficiency. Infants with Pompe disease have hypotonia, macroglossia, cardiomegaly, and hepatomegaly. Usually the infantile form is fatal. Adults suffer from slowly progressive myopathy with respiratory failure. Diaphragm, biceps, shoulder, and thigh adductor muscles are preferentially affected.

   The cause of this disorder is a mutation in the acid alpha-glucosidase gene (GAA), located on chromosome 17q25. GAA enzyme activity evaluation is diagnostic, but in borderline cases, molecular genetic testing is available.

   Treatment is now available for acid maltase deficiency, in the form of recombinant human α-glucosidase (Myozyme; Genzyme, Cambridge, MA, USA), given as repeated infusions. Enzyme replacement therapy has been clinically shown to lengthen the time before ventilator dependence in the infantile form. Adults have been documented to show increased strength and increased respiratory function.
2. **McArdle's disease,** or myophosphorylase deficiency, affects children and adults and manifests with myalgia, fatigue, and muscle stiffness. Myoglobinuria and renal failure can develop. CK level is increased. EMG shows changes supportive of myopathy.

TABLE 47-2 Metabolic Myopathies

Clinical Finding	Acid Maltase Deficiency	Myophosphorylase Deficiency	CPT II Deficiency
Gene defect	GAA	PYGM	CPT II
Age of onset	Infant–adult	Late childhood–adult	Adult
Muscle weakness	Progressive	Intermittent	Intermittent
Respiratory involvement	Yes	–	–
CK	Elevated	Elevated	Normal between attacks
Myoglobinuria	–	Yes	Yes
Electrical myotonia	Yes	–	–
Abnormal ischemic forearm exercise test	–	Yes: no rise in lactate	–
Muscle pathology	Vacuolar myopathy with elevated glycogen storage	Subsarcolemmal deposits of glycogen; absence of myophosphorylase staining	Normal or slight increase in lipid droplets in muscle fibers

(–), negative or absent.

The forearm ischemic exercise in affected patients shows no increase in venous lactate (as expected in normal controls). Muscle biopsy discloses subsarcolemmal deposits of glycogen. Immunohistochemistry staining of muscle biopsy tissue will show absence of myophosphorylase.

The disease is autosomal recessive, caused by homozygous or compound heterozygous mutations in the glycogen phosphorylase (PYGM) gene.

Prognosis is rather benign. Some patients can tolerate the deficits and learn to avoid brief, strong exercises that precipitate attacks. No definite treatment is available.

3. **Carnitine-O-palmitoyltransferase II (CPT II) deficiency** manifests in the adult patient with intermittent cramps, myalgia, and myoglobinuria. Renal failure, resulting from myoglobinuria, or respiratory failure may ensue. Between attacks, muscle strength is normal, CK and EMG are normal between attacks. The symptoms are precipitated by intense exertion. The capacity to perform short exercise is not impaired. Fasting, exposure to cold, high fat intake, viral infections, and general anesthesia can precipitate rhabdomyolysis. Increased lipid content may be seen on histochemical staining on muscle biopsy, but is not always present. The disease is autosomal recessive. The diagnosis is made by sequencing and mutation analysis of the carnitine palmitoyltransferase II (CPT2) gene. Therapy includes avoidance of triggers (general anesthesia, prolonged exercise, cold exposure and prolonged fasting) and a diet high in carbohydrates and low in fats.

VII. TOXIC MYOPATHY

Toxic myopathy is myopathy associated with either systemic disease or medication effect. Some medications produce direct muscle fiber necrosis, while others produce electrolyte imbalances with rhabdomyolysis. The most important types of toxic myopathy are **necrotizing, autophagic, antimicrotubular,** and **steroid.**

A. Natural history, prognosis, and treatment.

1. **Endocrine myopathy.**
   a. **Thyrotoxic myopathy** manifests as weakness and little muscle wasting. Fatigue and heat intolerance are also present. Hypokalemic periodic paralysis (see IV.2.a.) and myasthenia gravis are associated with hyperthyroidism and should be included in the differential diagnosis. Treatment relies on correcting the hyperthyroid state; ß-adrenergic blocking agents may be of help. Glucocorticoids should be used in thyroid storm to block the peripheral conversion of thyroxine in triiodothyronine.
   b. **Hypothyroid myopathy** manifests as enlargement of muscles, weakness, painful cramps, myoedema, and slow-recovery reflexes. This disease is more common among women. Rhabdomyolysis or respiratory muscle involvement may be present. Serum level of CK may be elevated. The diagnosis is supported by abnormal results of thyroid function tests. Treatment is to restore the euthyroid state.
2. **Toxic necrotizing myopathy.** The cholesterol-lowering drugs include 3-HMG-CoA reductase inhibitors (or statins) can cause a myopathy. Onset can be acute or insidious, often with myalgia, occasionally with myoglobinuria, and usually involving the proximal lower-extremity muscles. Patients with renal failure are especially predisposed. Elevated serum CK levels are common, and the EMG findings are abnormal. Muscle fiber necrosis with phagocytosis and small regenerating fibers are found on biopsy. When the medication is stopped, symptoms resolve in a few weeks to months. Asymptomatic elevations of CK level occur in about 1% of patients taking statins. **Cyclosporine** and **tacrolimus** have also been associated with toxic myopathy.
3. **Autophagic myopathy** occurs with **chloroquine** (and its derivatives), systemic lupus erythematosus, scleroderma, and rheumatoid arthritis, and with **amiodarone.** The myopathy of chloroquine affects the proximal lower-extremity muscles and is usually not painful. The course is subacute or chronic. The heart can be affected. Elevation in CK level and myotonic potentials on the EMG can be found. Muscle biopsy shows vacuoles (lysosomes), which stain for acid phosphatase and contain debris and curvilinear structures (autophagic vacuoles). With amiodarone, severe proximal and distal weakness may occur in combination with distal sensory loss, tremor, and ataxia. The treatment is to discontinue the medication.

4. **Antimicrotubular myopathy** is produced by **colchicine** and **vincristine.** These drugs bind to nerve and muscle tubulin. The toxic etiology of this myopathy is often not recognized because of the insidious onset in patients who may have been taking colchicine for years. Concomitant axonal sensorimotor neuropathy occurs. Weakness resolves slowly and may take 6 months after discontinuing the medication. Because of the neuromyopathy, a mixed pattern of denervation and myopathy is seen on electrophysiologic studies. Muscle biopsy shows acid-phosphatase-positive autophagic vacuoles.
5. The effects of **zidovudine** can be indistinguishable from the myopathy of HIV infection. It is due to mitochondrial toxicity associated with this agent. CK levels are normal or mildly elevated. Differentiation from AIDS myopathy can be difficult solely on a clinical basis. The muscle biopsy may show "ragged red fibers," a sign of mitochondrial disease, and its presence supports the diagnosis of zidovudine myopathy. Treatment consists of stopping the medication. Whereas myalgia (muscle pain) is usually relieved within weeks of discontinuing zidovudine, muscle weakness can persist for months.
6. **Steroid myopathy** is a type-2 fiber atrophy of muscles associated with long-term corticosteroid exposure. Doses of prednisone >30 mg per day carry the risk of myopathy. Fluorinated compounds (triamcinolone, betamethasone, and dexamethasone) have a greater risk. Patients have predominantly proximal muscle weakness and atrophy. Serum level of CK is usually normal. EMG findings are normal. Muscle biopsy shows type 2 fiber atrophy, especially type 2B (fast twitch glycolytic). Tapering to an alternate-day regimen, use of "steroid-sparing" drugs (e.g., azathioprine), use of nonfluorinated steroids, and exercise may reduce the incidence of this myopathy.

   In poly- or dermatomyositis, clinical worsening in a patient being treated with steroids may represent either a progression of the primary disease or the onset of steroid myopathy. The decision to raise or lower the prednisone dose has to be made after careful evaluation of the patient's muscle strength, mobility, CK levels, and medication changes in the preceding months.

Recommended Readings

Amato AA, Darras BT, Greenberg SA, et al. Muscle diseases. *AAN Continuum*. 2006;12(3): 140–168.

Brooke MH. *A Clinician's View of Neuromuscular Diseases*. Baltimore, MD: Williams & Wilkins; 1986.

Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet*. 2003;362(9388):971–982.

Griggs RC. Periodic paralysis. In: Wilson JD, et al., Wilson JD, Braunwald E, Isselbacher KJ et al., eds. *Harrison's Principles of Internal Medicine*. 12th ed. New York, NY: McGraw-Hill; 1991:2121.

Griggs RC, Mendell JR, Miller RG. *Evaluation and Treatment of Myopathies*. Philadelphia, PA: FA Davis Co; 1995.

Jurkat-Rott K, Lehmann-Horn F. Paroxysmal muscle weakness: the familial periodic paralyses. *J Neurol*. 2006;253(11):1391–1398.

Kirschner J, Bonnemann CG. The congenital and limb-girdle muscular dystrophies: sharpening the focus, blurring the boundaries. *Arch Neurol*. 2004;61(2):189–199.

Machuca-Tzill L, Brook D, Hilton-Jones D. Clinical and molecular aspects of the myotonic dystrophies: a review. *Muscle Nerve*. 2005;32:1–18.

Mastaglia FL, Phillips BA, Zilko P. Treatment of inflammatory myopathies. *Muscle Nerve*. 1997;20:651–664.

Walsh RJ, Amato AA. Toxic myopathies. *Neurol Clin*. 2005;23:397–428.

CHAPTER

48 Disorders of the Neuromuscular Junction

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I. MYASTHENIA GRAVIS

Myasthenia gravis (MG) is an autoimmune disorder of neuromuscular transmission involving the production of autoantibodies directed against the nicotinic acetylcholine (ACh) receptor. ACh receptor antibodies are detectable in the serum of 80% to 90% of patients with MG. The prevalence of MG is about 1 in 10,000 to 20,000 persons. Women are affected about twice as often as men. Symptoms may begin at virtually any age with a peak in women in the second and third decades, whereas the peak in men occurs in the fifth and sixth decades. Associated autoimmune diseases such as rheumatoid arthritis, lupus, and pernicious anemia are present in about 5% of patients. Thyroid disease occurs in about 10%, often in association with anti-thyroid antibodies. About 10% to 15% of MG patients have a thymoma, whereas thymic lymphoid hyperplasia with proliferation of germinal centers occurs in 50% to 70% of cases. In most patients, the cause of autoimmune MG is unknown. However, there are three iatrogenic causes for autoimmune MG. D-penicillamine (used in the treatment of Wilson's disease and rheumatoid arthritis) and α-interferon therapy are both capable of inducing MG. In addition, bone marrow transplantation is associated with the development of MG as part of the chronic graft versus host disease.

A. Clinical features. The hallmark of MG is fluctuating or fatigable weakness. The presenting symptoms are ocular in half of all patients (25% of patients initially present with diplopia, 25% with ptosis), and by 1 month into the course of illness, 80% of patients have some degree of ocular involvement. Presenting symptoms are bulbar (dysarthria or dysphagia) in 10%, leg weakness (impaired walking) in 10%, and generalized weakness in 10%. Respiratory failure is the presenting symptom in 1% of cases. Patients usually complain of symptoms from focal muscle dysfunction such as diplopia, ptosis, dysarthria, dysphagia, inability to work with arms raised over the head, or disturbance of gait. In contrast, patients with MG tend not to complain of "generalized weakness," "generalized fatigue," "sleepiness," or muscle pain. In the classic case, fluctuating weakness is worse with exercise and improved with rest. Symptoms tend to progress later in the day. Many different factors can precipitate or aggravate weakness, such as physical stress, emotional stress, infection, or exposure to medications that impair neuromuscular transmission (perioperative succinylcholine, aminoglycoside antibiotics, quinine, quinidine, and botulinum toxin).

B. Diagnosis. The diagnosis is based on a history of fluctuating weakness with corroborating findings on examination. There are several different ways to validate or confirm the clinical diagnosis.

1. **Edrophonium (Tensilon) test.** The most immediate and readily accessible confirmatory study is the edrophonium (Tensilon) test. To perform the test, choose 1 or 2 weak muscles to judge. Ptosis, dysconjugate gaze, and other cranial deficits provide the most reliable endpoints. Use a setting where hypotension, syncope, or respiratory failure can be managed as patients occasionally decompensate during the test. If the patient has severe dyspnea, defer the test until the airway is secure. Start an intravenous (IV). Have IV atropine 0.4 mg readily available in the event of bradycardia or extreme gastrointestinal (GI) side effects. Edrophonium 10 mg (1 ml) is drawn up in a syringe, and 1 mg (0.1 ml) should be given as a test dose while checking the patient's heart rate (to assure the patient is not supersensitive to the drug). If no untoward side effects occur after 1 minute, another 3 mg is given. Many MG patients will show improved power within 30 to 60 seconds of giving the initial 4 mg at which point the test can be stopped. If after 1 minute there is no improvement, give additional 3 mg, and if there is still no response, 1 minute later give the final 3 mg. If the patient develops muscarinic symptoms or signs at any time

during the test (sweating, salivation, and GI symptoms), or should fasciculations be detected then one can assume that enough edrophonium has been given to see improvement in strength and the test can be stopped. When a placebo effect or examiner bias is of concern, the test is performed in a double-blind placebo control fashion. The 1 ml control syringe contains either saline, 0.4 mg atropine, or nicotinic acid 10 mg. Improved strength from edrophonium lasts for just a few minutes. When improvement is clear-cut, the test is positive. If the improvement is borderline, it is best to consider the test negative. The test can be repeated several times. Sensitivity of the edrophonium test is about 90%. The specificity is difficult to determine because improvement following IV edrophonium has been reported in other neuromuscular diseases including Lambert–Eaton's syndrome (LES), botulism, Guillain–Barré syndrome, motor neuron disease, and with lesions of the brainstem, pituitary, and cavernous sinus. Neostimine has a longer duration of effect and in selected patients may be an alternative cholinesterase inhibitor (CEI) for diagnostic testing, especially in children. For performance of a "neostigmine test," 0.04 mg per kg is given intramuscularly or 0.02 mg per kg intravenously (one time only).

2. **ACh receptor antibodies.** The primary serologic test is the immunoprecipitation assay for ACh receptor binding antibodies. In addition, assays for receptor modulating and blocking antibodies are available. Binding antibodies are present in about 80% of all myasthenia patients (40% to 50% of patients with pure ocular MG, 80% of those with mild generalized MG, and 90% of patients with moderate to severe generalized MG, and 70% of those in clinical remission). By also testing for modulating and blocking antibodies, the sensitivity improves to 90% overall. Specificity is superb with false positives exceedingly rare in reliable labs.
3. **MuSK antibodies.** Approximately 25% of patients seronegative for ACh receptor antibodies have antibodies to muscle specific kinase (MuSK). The clinical features of MuSK positive patients may differ from non-MuSK MG patients. Such patients tend to be younger women (under age 40) with disproportionate bulbar, neck extensor, shoulder, and respiratory symptoms with increased likelihood of "fixed weakness" and have a lower likelihood of abnormal repetitive stimulation and edrophonium test results. MuSK patients have no associate thymus abnormalities and are more likely to be refractory to medical management.
4. **EMG (electrophysiological testing).** Repetitive stimulation testing is widely available and has variable sensitivity depending on the number and selection of muscles studied and various provocative maneuvers. However, in most labs this technique has a sensitivity of about 50% in all patients with MG (lower in patients with mild or pure ocular disease). In general, the yield from repetitive stimulation is higher when testing muscle groups having clinically significant weakness. Single fiber EMG (SFEMG) is a highly specialized technique, usually available in major academic centers, with a sensitivity of about 90%. Abnormal single fiber results are common in other neuromuscular diseases; therefore, the test must be used in the correct clinical context. The specificity of SFEMG is an important issue in that mild abnormalities can clearly be present with a variety of other diseases of the motor unit including motor neuron disease, peripheral neuropathy, and myopathy. Disorders of neuromuscular transmission other than MG can have abnormalities on SFEMG. In contrast, ACh receptor antibodies (and MuSK antibodies) are not found in non-MG patients. In summary, the two highly sensitive laboratory studies are SFEMG and ACh receptor antibodies; nonetheless, neither test is 100% sensitive.

C. **Prognosis.** Natural course: Appropriate management of the patient with autoimmune MG requires understanding of the natural course of the disease. The long-term natural course of MG is highly variable but generalizations are as follows. About half of MG patients present with ocular symptoms (ptosis or diplopia) and by 1 month 80% have eye findings. The presenting weakness is bulbar in 10%, limb in 10%, generalized in 10%, and respiratory in 1%. By 1 month symptoms remain purely ocular in 40%, generalized in 40%, limited to the limbs in 10%, and limited to bulbar muscles in 10%. Weakness remains restricted to the ocular muscles on a long-term basis in about 15% to 20% (pure ocular MG). Most patients with initial ocular involvement tend to develop generalized weakness within the first year of the disease (90% of those who generalize do so within the initial 12 months). Maximal weakness occurs within the initial 3 years

in 70% of patients. In the modem era, death from MG is rare. Spontaneous long-lasting remission occurs in about 10% to 15%, usually in the first or second year of the disease. Most MG patients develop progression of clinical symptoms during the initial 2 to 3 years. However, progression is not uniform, as illustrated by 15% to 20% of patients whose symptoms remain purely ocular and those who have spontaneous remission.

D. Treatment.

1. **First-line therapy:** CEIs are safe, effective, and first-line therapy in all patients. Inhibition of acetylcholinesterase (AChE) reduces the hydrolysis of ACh, increasing the accumulation of ACh at the nicotinic postsynaptic membrane. The CEIs used in MG bind reversibly (as opposed to organophosphate CEIs, which bind irreversibly) to AChE. These drugs cross the blood–brain barrier poorly and tend not to cause CNS side effects. Absorption from the GI tract tends to be inefficient and variable, with oral bioavailability of about 10%. Muscarinic autonomic side effects of GI cramping, diarrhea, salivation, lacrimation, diaphoresis are common and dose-related, and occasional patients may have bradycardia. A feared potential complication of excessive CEI use is skeletal muscle weakness (cholinergic weakness). Patients receiving parenteral CEI are at the greatest risk to have cholinergic weakness. It is uncommon for patients receiving oral CEI to develop significant cholinergic weakness even while experiencing muscarinic cholinergic side effects. Generally available CEIs are summarized in Table 48.1.
   a. Pyridostigmine (Mestinon) is the most widely used CEI for long-term oral therapy. Onset of effect is within 30 minutes of an oral dose, with peak effect within 1 to 2 hours, and wearing off gradually at 3 to 4 hours post-dose. The starting dose is 30 to 60 mg three to four times per day depending on symptoms. Optimal benefit usually occurs with a dose of 60 mg every 4 hours. Muscarinic cholinergic side effects are common with larger doses. Patients with significant bulbar weakness will often time their dose about 1 hour before meals in order to maximize chewing and swallowing. Of all the CEI preparations, pyridostigmine has the least muscarinic side effects. Pyridostigmine may be used in a number of alternative forms to the 60 mg tablet. The syrup may be necessary for children or for patients with difficulty swallowing pills. Sustained-release pyridostigmine 180 mg (Mestinon Timespan) is sometimes preferred for night time use. Unpredictable release and absorption limit its use. Patients with severe dysphagia or those undergoing surgical procedures may need parenteral CEI. IV pyridostigmine should be given at about 1/30 of the oral dose.

TABLE 48.1 Cholinesterase Inhibitors

	Unit Dose	Average Dose (Adult)
Pyridostigmine bromide tablet (Mestinon)	60 mg tablet	30–60 mg every 4–6 hr
Pyridostigmine bromide syrup	12 mg/ml	30–60 mg every 4–6 hr
Pyridostigmine bromide timespan (Mestinon Timespan)	180 mg tablet	1 tablet twice daily
Pyridostigmine bromide (Parenteral)	5 mg/ml ampoules	1–2 mg every 3–4 hr (1/30 of oral dose)
Neostigmine bromide (Prostigmin)	15 mg tablet	7.5–15 mg every 3–4 hr
Neostigmine methylsulfate (Parenteral)	0.25–1.0 mg/ml	0.5 mg IM, IV, or SC ampoules every 2–3 hr

Children's dosing:

Edrophonium (Tensilon)

Diagnosis: 0.1 mg/kg IV (or 0.15 mg/kg IM or SC, which prolongs the effect), preceded by a test dose of 0.01 mg/kg

Pyridostigmine bromide (Mestinon)

Treatment: oral dose is about 1.0 mg/kg every 4–6 hr, as tablets or syrup (60 mg/5 ml)

Neostigmine methylsulfate (Parenteral)

Diagnosis: 0.1 mg/kg/ IM or SC X1 or 0.05 mg/kg/ IV X1

Treatment: 0.01–0.04 mg/kg/dose IM, IV, or SC q 2–3 hr p.r.n.

Abbreviations: IM, intramuscular; SC, subcutaneous; p.r.n., as needed.

Neostigmine (prostigmine) has a slightly shorter duration of action and somewhat greater muscarinic side effects.

b. For patients with intolerable muscarinic side effects at CEI doses required for optimal power, a concomitant anticholinergic drug such as atropine sulfate (0.4 to 0.5 mg orally) or glycopyrrolate (Robinul) (1 to 2 mg orally) on a p.r.n. basis or with each dose of CEI may prevent the side effects. Patients with mild disease can often be managed adequately with CEIs. However, patients with moderate, severe, or progressive disease will usually require more effective therapy.

2. **Thymectomy:** Association of the thymus gland with MG was first noted around 1900 and thymectomy has become standard therapy for over 50 years. As the benefit from thymectomy is anecdotal and controversial, a large randomized international multicenter controlled trial is currently in progress. Until the completion of that study, the general consensus is that thymectomy should be considered for patients with moderate to severe MG, especially those inadequately controlled on CEI, and those under age 55 years. All patients with suspected thymoma undergo surgery. About 75% of MG patients appear to benefit from thymectomy. Patients may improve or simply stabilize. For unclear reasons, the onset of improvement tends to be delayed by a year or two in most patients (some patients may improve 5 to 10 years after surgery). The majority of centers use the transsternal approach for thymectomy with the goal of complete removal of the gland. The limited transcervical approach has been largely abandoned due to the likelihood of incomplete gland removal. Many centers perform a "maximal thymectomy" in order to ensure complete removal. The procedure involves a combined transternal–transcervical exposure with en bloc removal of the thymus. Thorascopic and video-assisted thymectomy offer less invasive options. If thymectomy is to be performed, choose an experienced surgeon, anesthesiologist, and center with a good track record and insist that the entire gland is removed.

   a. Which patients do not undergo thymectomy? Patients with very mild or trivial symptoms do not have surgery. Most patients with pure ocular MG do not undergo thymectomy even though there has been some reported benefit in selected patients. Thymectomy is often avoided in children due to the theoretical possibility of impairing the developing immune system. However, reports of thymectomy in children as young as 2 to 3 years of age have shown favorable results without adverse effects on the immune system. Thymectomy has been largely discouraged in patients over age 55 because of expected increased morbidity, latency of clinical benefit, and frequent observation of an atrophic, involuted gland. Major complications from thymectomy are uncommon so long as the surgery is performed at an experienced center with anesthesiologists and neurologists familiar with the disease and perioperative management of MG patients. Common, though less serious, aspects of thymectomy include postoperative chest pain (which may last several weeks), a 4- to 6-week convalescence period, and cosmetically displeasing incisional scar.

3. **Corticosteroids.** There are no controlled trials documenting the benefit of corticosteroids in MG. However, nearly all authorities have personal experience attesting to the virtues (and complications) of corticosteroid use in MG patients. In general, corticosteroids are used in patients with moderate to severe disabling symptoms that are refractory to CEI. Patients are commonly hospitalized to initiate therapy due to the risk of early exacerbation. Opinions differ regarding the best method of administration. For patients with severe MG it is best to begin with high-dose daily therapy of 60 to 80 mg per day orally. Early exacerbation occurs in about half of patients, usually within the first few days of therapy and typically lasting 3 or 4 days. In 10% of cases, the exacerbation is severe, requiring mechanical ventilation or a feeding tube (thus, the need to initiate therapy in the hospital). Overall, about 80% of patients show a favorable response to steroids (with 30% attaining remission and 50% having marked improvement). Mild to moderate improvement occurs in 15%, and 5% have no response. Improvement begins as early as 12 hours and as late as 60 days after beginning prednisone, but usually the patient begins to improve within the first or second week. Improvement is gradual, with marked improvement occurring at a mean of 3 months, and maximal improvement at a mean of 9 months. Of those patients having a favorable response, most maintain their improvement with gradual dosage reduction at a rate of 10 mg every 1 to 2 months.

More rapid reduction is usually associated with a flare-up of the disease. Although many patients can eventually be weaned off steroids and maintain their response, the majority cannot. They require a minimum dose (5 to 30 mg alternate day [AD]) in order to maintain their improvement. Complications of long-term high-dose prednisone therapy are substantial, including cushingoid appearance, hypertension, osteoporosis, diabetes, cataracts, aseptic necrosis, and the other well-known complications of chronic steroid therapy. Older patients tend to respond more favorably to prednisone. An alternative prednisone regimen involves low-dose AD gradually increasing schedule in an attempt to avoid the early exacerbation. Patients receive prednisone 25 mg AD with increase by 12.5 mg every third dose (about every fifth day) to a maximum dose of 100 mg AD or until sufficient improvement occurs. Clinical improvement usually begins within 1 month of treatment. The frequency and severity of early exacerbation is less than that associated with high-dose daily regimens. High-dose IV methylprednisolone (1,000 mg IV daily for 3 to 5 days) can provide improvement within 1 to 2 weeks but the clinical improvement is temporary.

4. **Alternative immunosuppressive drug therapy.**
   a. **Mycophenolate mofetil** (CellCept) is a purine inhibitor widely used in recent years for the treatment of MG. Anecdotal uncontrolled experience would suggest that about 75% of MG patients benefit from the drug with the typical onset of improvement within 2 to 3 months. The drug is generally well tolerated. Typically begin with 250 to 500 mg orally twice a day, and over 2 to 4 weeks increase the dose to 1,000 mg orally twice a day. Two recently completed prospective controlled double-blind trials failed to demonstrate a benefit from mycophenolate in selected MG patients leading to a reevaluation of its role and suggesting that the anecdotal reports of benefit may be incorrect. Complications are uncommon and include GI intolerance and occasional patients with hepatic or hematological abnormalities.
   b. **Azathioprine** (Imuran) is a cytotoxic purine analog with extensive use in MG (but largely uncontrolled and retrospective). The starting dose is 50 mg by mouth daily, with CBC and liver function tests weekly in the beginning. If the drug is tolerated and if the blood work is stable, the dose is increased by 50 mg every 1 to 2 weeks aiming for a total daily dose or about 2 to 3 mg/kg/day (about 150 mg/day in the average-sized adult). When azathioprine is first started, about 15% of patients will have intolerable GI side effects (nausea, anorexia, and abdominal discomfort) and sometimes associated with fever, leading to discontinuation. Bone marrow suppression with relative leukopenia (WBC 2,500 to 4,000) occurs in 25% of patients but is usually not significant. If the WBC drops below 2,500 or the absolute granulocyte count goes below 1,000, the drug is stopped (and the abnormalities usually resolve). Macrocytosis is common and of unclear clinical significance. Liver enzymes elevate in 5% to 10% but are usually reversible, and severe hepatic toxicity occurs in only about 1%. Infection occurs in about 5%. There is a theoretical risk of malignancy (based on observations in organ transplant patients), but this increased risk has not been clearly established in the MG patient population. About half of MG patients improve on azathioprine with onset about 4 to 8 months into treatment. Maximal improvement takes about 12 months. Relapse after discontinuation of azathioprine occurs in over half of patients, usually within 1 year.
   c. **Cyclosporine** is used in patients with severe MG who cannot be adequately managed with corticosteroids or azathioprine. The starting dose is 3 to 5 mg/kg/day given in two divided doses. Cyclosporine blood levels should be measured monthly (aiming for a level of 200 to 300) along with electrolytes, magnesium, and renal function (in general, serum creatinine should not exceed one and one-half times the pretreatment level). Blood should be sampled before the morning dose is taken. Over half of patients improve on cyclosporine. The onset of clinical improvement occurs about 1 to 2 months after beginning therapy, and maximal improvement occurs at about 3 to 4 months. Side effects include renal toxicity and hypertension. Nonsteroidal anti-inflammatory drugs and potassium-sparing diuretics are among the list of drugs that should be avoided while on cyclosporine. In patients on corticosteroids, the addition of cyclosporine can lead to a reduction in steroid dosage (although it is usually not possible to discontinue prednisone).

d. **Methotrexate** has been used in selected patients for decades with clinical response the subject of sporadic anecdotal reports. Currently a large prospective multicenter study of methotrexate in myasthenia is under way to clarify its value in treatment.
e. **Tacrolimus** has been reported to be beneficial in several series and in some parts of the world is among the more commonly prescribed immunosuppressive options.
f. **Rituximab** has been reported to be effective in treating MG in selected patients (the anecdotal reports tend to involve relatively refractory patients who have done poorly with alternative treatment options). The anecdotal reports of rituximab benefits in MuSK patients are particularly notable given the disproportionate tendency for such patients to be refractory to many other immunosuppressive options.

5. **Plasma exchange** (plasmapheresis) removes ACh receptor antibodies and results in rapid clinical improvement. The standard course involves removal of 2 to 3 L of plasma every other day or 3 times per week until the patient improves (usually a total of three to five exchanges). Improvement begins after the first few exchanges and reaches the maximum within 2 to 3 weeks. The improvement is moderate to marked in nearly all patients but usually wears off after 4 to 8 weeks due to the re-accumulation of pathogenic antibodies. Vascular access may require placement of a central line. Complications include hypotension, bradycardia, electrolyte imbalance, hemolysis, infection, and access problems (such as pneumothorax from placement of a central line). Indications for plasma exchange include any patient in whom a rapid temporary clinical improvement is needed.
6. **High-dose IV and subcutaneous immunoglobulin (IVIG)** administration is associated with rapid improvement in MG symptoms in a time frame similar to plasma exchange. The mechanism is unclear but may relate to down-regulation of ACh receptor antibody production or to the effect of anti-idiotype antibodies. The usual protocol is 2 g/kg spread out over 5 consecutive days (0.4 g/kg/day). Different IVIG preparations are administered IV at different rates (contact the pharmacy for guidelines). The majority of MG patients improve, usually within 1 week of starting IVIG. The degree of response is variable and the duration of response is limited, as with plasma exchange, to about 4 to 8 weeks. Complications include fever, chills, and headache, which respond to slowing down the rate of the infusion and giving diphenhydramine. Occasional cases of aseptic meningitis, renal failure, nephrotic syndrome, and stroke have been reported. Also, patients with selective IgA deficiency can have anaphylaxis, best avoided by screening for IgA deficiency ahead of time. The treatment is relatively expensive, comparable to plasma exchange. In patients with problematic IV access or those using IG for long-term maintenance therapy a subcutaneous IG preparation is an alternative.

E. General guidelines for management.

1. **Be certain of the diagnosis.**
2. **Patient education.** Provide the patient with information about the natural course of the disease (including the variable and somewhat unpredictable course). Briefly review the treatment options outlined above pointing out effectiveness, time course of improvement, duration of response, and complications. Provide the patient with educational pamphlets prepared by the Myasthenia Gravis Foundation or the Muscular Dystrophy Association.
3. **When to hospitalize the patient.** Patients with severe MG can deteriorate rapidly over a period of hours. Therefore, those having dyspnea should be hospitalized immediately in a constant observation or intensive care setting. Patients with moderate or severe dysphagia, weight loss, as well as those with rapidly progressive or severe weakness should be admitted urgently. This will allow close monitoring and early intervention in the case of respiratory failure and will also expedite the diagnostic workup and initiation of therapy.
4. Myasthenic crisis (Table 48.2) is a medical emergency characterized by respiratory failure from diaphragm weakness or severe oropharyngeal weakness leading to aspiration. Crisis can occur in the setting of surgery (post-op), acute infection, or following rapid withdrawal of corticosteroids (though some patients have no precipitating factors). Patients should be placed in an intensive care unit (ICU) setting and have forced vital capacity (FVC) checked every 2 hours. Changes in arterial blood gases occur relatively late in neuromuscular respiratory failure. There should be a low threshold for intubation

TABLE 48.2 The Acutely Deteriorating Myasthenic Patient

Myasthenic crisis	Cholinergic crisis
Respiratory distress	Abdominal cramps
Respiratory arrest	Diarrhea
Cyanosis	Nausea and vomiting
Increased pulse and blood pressure	Excessive secretions
Diaphoresis	Miosis
Poor cough	Fasciculations
Inability to handle oral secretions	Diaphoresis
Dysphagia	Weakness
Weakness	Worse with edrophonium
Improves with edrophonium	

and mechanical ventilation. Criteria for intubation include a drop in the FVC below 15 ml per kg (or below 1 L in an average-sized adult), severe aspiration from oropharyngeal weakness, or labored breathing regardless of the measurements. If the diagnosis is not clear-cut, it is advisable to secure the airway with intubation, stabilize ventilation, and only then address the question of the underlying diagnosis. If the patient has been taking CEI, the drug should be temporarily discontinued in order to rule out the possibility of "cholinergic crisis."

5. Screen for and correct any underlying medical problems such as systemic infection, metabolic problems (like diabetes), and thyroid disease (hypo- or hyperthyroidism can exacerbate MG).
6. Drugs to avoid in MG. Avoid using D-penicillamine, α-interferon, chloroquine, quinine, quinidine, procainamide, and botulinum toxin. Aminoglycoside antibiotics should be avoided unless needed for a life-threatening infection. Fluoroquinolones (ciprofloxacin) and erythromycin have significant neuromuscular blocking effects. Telithromycin (Ketek) has been reported to cause life-threatening weakness in patients with MG and should not be used. Neuromuscular blocking drugs such as pancuronium and D-tubocurarine can produce marked and prolonged paralysis in MG patients. Depolarizing drugs such as succinylcholine can also have a prolonged effect and should be used by a skilled anesthesiologist who is well aware of the patient's MG.

F. Guidelines for specific therapies. Treatment must be individualized. Mild diplopia and ptosis may not be disabling for some patients, but for a pilot or neurosurgeon, mild intermittent diplopia may be critical. In a similar fashion, some patients may tolerate side effects better than others.

1. Mild or trivial weakness, either localized or generalized, should be managed with a CEI pyridostigmine.
2. Moderate to marked weakness, localized or generalized, should initially be managed with CEI. Even if symptoms are adequately controlled, patients under age 55 should be considered for thymectomy early in the course of the disease (within the first year). In older patients, thymectomy is usually not performed unless the patient is thought to have a thymoma. Thymectomy is performed at an experienced center with the clear intent of complete removal of the gland. All patients with suspected thymoma (by chest scan) should have thymectomy, even if their myasthenic symptoms are mild. Unless a thymoma is suspected, patients with pure ocular disease are usually not treated with thymectomy.
3. If symptoms are inadequately controlled on CEI, immunosuppression is used. High-dose corticosteroid therapy is the most predictable and effective long-term option. If patients have severe, rapidly progressive, or life-threatening symptoms, the decision to start corticosteroids is clear-cut. Patients with disabling but stable symptoms may instead receive a nonsteroidal immunosuppressive drug such as azathioprine.
4. Plasma exchange or IVIG are indicated in:
   a. Rapidly progressive, life-threatening, impending myasthenic crisis or actual crisis, particularly if prolonged intubation with mechanical ventilation is judged hazardous.

b. Preoperative stabilization of MG (such as prior to thymectomy or other elective surgery) in poorly controlled patients.
c. Disabling MG refractory to other therapies (maintenance therapy).

5. If these options fail, then use mycophenolate, cyclosporine, tacrolimus, or rituximab.
6. If the patient remains poorly controlled despite appropriate treatment, then perform a repeat chest CT scan looking for residual thymus. Some patients improve after "repeat thymectomy." Check for other medical problems (diabetes, thyroid disease, infection, and coexisting autoimmune diseases).
7. Referral to a neurologist or center specializing in neuromuscular disease is advised for all patients with suspected MG and can be particularly important for complicated or refractory patients.

G. Transient neonatal myasthenia occurs in 10% to 15% of babies born to mothers with autoimmune MG. Within the first few days after delivery the baby has a weak cry or suck, appears floppy, and on occasion, requires mechanical ventilation. The condition is caused by maternal antibodies that cross the placenta late in pregnancy. As these maternal antibodies are replaced by the baby's own antibodies, the symptoms gradually disappear, usually within a few weeks, and the baby is normal thereafter. Infants with severe weakness are treated with oral pyridostigmine 1 to 2 mg per kg every 4 hours.

H. Congenital myasthenia represents a group of rare hereditary disorders of the neuromuscular junction. The patients tend to have lifelong relatively stable symptoms of generalized fatigable weakness. These disorders are nonimmunologic, without ACh receptor antibodies, and therefore patients do not respond to immune therapy (steroids, thymectomy, and plasma exchange). Most of these patients improve on CEI. Even though there are many established subtypes of congenital myasthenia gravis, several are worth noting due in part to specific therapeutic implications. The **fast channel congenital myasthenic syndrome** tends to be static or slowly progressive, but usually very responsive to combination therapy with 3,4-diaminopyridine (enhances release of ACh) and pyridostigmine (reduces metabolism of ACh). **Slow channel congenital myasthenic syndrome** typically worsens over years as the endplate myopathy progresses. Although CEIs typically worsen symptoms, quinidine and fluoxetine, which reduce the duration of ACh receptor channel openings, are both effective treatments for slow channel syndrome. **The congenital myasthenic syndrome associated with ACh receptor deficiency** tends to be relatively nonprogressive and may even improve slightly as the patient ages. The disorder typically responds to symptomatic therapy with pyridostigmine and/or 3,4-diaminopyridine. Ephedrine produces benefit in some cases. **Patients with endplate AChE deficiency** usually present in infancy or early childhood with generalized weakness, underdevelopment of muscles, slowed pupillary responses to light, and either no response or worsening with CEIs. No effective long-term treatment has been described for congenital endplate AChE deficiency.

II. LAMBERT–EATON'S SYNDROME

LES (myasthenic syndrome) is a presynaptic disease characterized by chronic fluctuating weakness of proximal limb muscles. Symptoms include difficulty walking, climbing stairs, or rising from a chair. In LES there may be some improvement in power with sustained or repeated exercise. In contrast, eyelid ptosis, diplopia, dysphagia, and respiratory failure are far less common. In addition, LES patients often complain of myalgias, muscle stiffness of the back and legs, distal paresthesias, metallic taste, dry mouth, impotence, and other autonomic symptoms of muscarinic cholinergic insufficiency. LES is rare compared to MG, which is about 100 times more common. About half of LES patients have an underlying malignancy that is usually small-cell carcinoma of the lung. In patients without malignancy, LES is an autoimmune disease and can be associated with other autoimmune phenomena. In general, patients over age 40 are more likely to be men and have an associated malignancy whereas younger patients are more likely to be women and have no neoplasm malignancy. LES symptoms can precede detection of the malignancy by 1 to 2 years.

A. The examination typically shows proximal lower extremity weakness, although the objective bedside assessment may suggest relatively mild weakness relative to the patient's history. The muscle stretch reflexes are absent. On testing sustained maximal grip there is a gradual increase in power over the initial 2 to 3 seconds (Lambert's sign).

B. The **diagnosis** is confirmed with EMG studies, which typically show low amplitude of the compound muscle action potentials and a decrement to slow rates or repetitive stimulation. Following brief exercise, there is marked facilitation of the compound motor action potential (CMAP) amplitude. At high rates of repetitive stimulation, there may be an incremental response. SFEMG is markedly abnormal in virtually all patients with LES. The pathogenesis involves auto-antibodies directed against voltage-gated calcium channels at cholinergic nerve terminals. These IgG antibodies also inhibit cholinergic synapses of the autonomic nervous system. Over 90% of LES patients demonstrated these antibodies to voltage-gated calcium channels in serum, providing another useful diagnostic test.

C. **Treatment.**

1. In patients with associated malignancy, successful treatment of the tumor can lead to improvement in the LES symptoms if the malignancy is successfully treated.
2. Symptomatic improvement in neuromuscular transmission may occur with the use of CEIs such as pyridostigmine.
3. 3,4-Diaminopyridine (DAP) increases ACh release by blocking voltage dependent potassium conductance and thereby prolonging depolarization at the nerve terminal and enhancing the voltage dependent calcium influx. 3,4-DAP has been shown to clearly improve most patients with LES with relatively mild toxicity and is becoming increasingly available, such that it represents first-line symptomatic therapy for LES. The typical beginning dose is 10 mg every 4 to 6 hours with gradual increase as needed up to a maximum of 100 mg per day.
4. Immunosuppressive therapy is used in patients with disabling symptoms. Long-term high-dose corticosteroids, plasma exchange, and IVIG have all been used with moderate success. In general, the use of these therapies should be tailored to the severity of patient's symptoms.

III. BOTULISM

Consumption of sausage spoiled by *Clostridium botulinum* resulted in an outbreak of this paralytic illness in the 1700s in Germany, leading to the name botulism, derived from the Latin term for sausage, *botulus*. Botulinum toxin blocks ACh release at the presynaptic motor nerve terminal (and causes dysautonomia by blocking muscarinic autonomic cholinergic function as well). The intracellular target of botulinum toxin appears to be a protein of the ACh vesicle membrane. The toxin is a zinc-dependent protease that cleaves protein components of the neuroexocytosis apparatus.

A. **Classic botulism** occurs after ingestion of food contaminated by botulinum toxin. Eight different toxins have been identified, but disease in humans is caused by types A, B, and E. Type E is associated with contaminated seafood. All types produce a similar clinical picture, although type A may produce more severe and enduring symptoms. In all three types, the condition is potentially fatal. Most cases result from ingestion of bottled or canned foods that have not been properly sterilized during preparation, especially "home-canned foods." Today's tomatoes used in home canning may have a low acid content as compared to the "good old days," and therefore may be more vulnerable for contamination. Foods cooked on an outdoor grill and then wrapped in foil for a day or two, creating an anaerobic environment, can lead to toxin production. Home-bottled oils should also be considered; in the case of children, honey may be contaminated.

1. **Clinical features** begin 12 to 48 hours after ingestion of tainted food. Bulbar symptoms including diplopia, ptosis, blurred vision, dysarthria, and dysphagia occur initially, and are followed by weakness in the upper limbs and then in the lower limbs. In contrast to the typical patient with Guillain–Barré syndrome, botulism is sometimes said to produce an acute "descending paralysis." Severe cases result in respiratory failure

requiring mechanical ventilation. Botulism produces autonomic dysfunction, including constipation, ileus, dry mouth, and dilated pupils (note: some of these signs are seen in most but not all patients; normal pupils do not rule out the diagnosis of botulism).

2. **Diagnosis.** The CMAP amplitudes are typically low on the motor nerve conduction studies. Repetitive stimulation studies before and following exercise may show a decrement to low rates of repetitive stimulation and postexercise facilitation of the CMAP amplitude. It is wise to send both stool and serum specimens to the lab for detection of the toxin. The specimen is injected into the peritoneum of a mouse, while neutralized or inactivated specimen is injected as the control. If the mouse becomes paralyzed and dies, the diagnosis is secure. Toxin is found in blood samples 30% to 40% of the time, while stool samples have a somewhat higher yield (thus the need to send both). Newer polymerase chain reaction tests for the clostridial genes and ELISA identification of the toxin have been used to screen for the bacteria in food but are not widely available for clinical usage.
3. **Management** involves placement of the patient in the ICU and assiduous monitoring of pulmonary function every few hours. When the FVC falls below 15 ml per kg or below 1 L or if the patient appears to be having respiratory difficulty, intubation and mechanical ventilation are necessary.
   a. There is a **trivalent botulinum antitoxin,** but its use is inconsistent, in part because of adverse side effects that occur in about 10% to 20% of patients. There is some evidence that the antitoxin shortens the course of the illness, especially the one associated with type E. If a diagnosis can be made early, it may be worth using the antitoxin. Serious complications from antitoxin therapy include serum sickness (4%), urticaria (3%), and anaphylaxis (2%).
   b. CDC recommends administration of one vial of antitoxin for adult patients with botulism as soon as diagnosis is made, without waiting for laboratory confirmation; before administration of antitoxin, consider skin testing for sensitivity to serum or antitoxin. One vial of trivalent botulism antitoxin administered IV results in serum levels of type A, B, and E antibodies capable of neutralizing serum toxin concentrations in excess of those reported for botulism patients.
   c. Antitoxin packages, including instructions for skin or conjunctival testing for hypersensitivity, are available through the CDC and state health departments. Antitoxin neutralizes toxin not yet bound to nerve terminals and has circulating half-life of 5 to 8 days. Patients who do not receive antitoxin treatment show free toxin in serum for up to 28 days.
4. **Clinical course.** With aggressive support, the overall mortality remains about 5% to10%, usually the result of respiratory or septic complications. The other patients improve over a period of several weeks to several months. In those who survive, the eventual level of recovery usually is nearly complete. Several years after the illness, some patients have subjective fatigue and autonomic symptoms including constipation, impotence, and dry mouth. Clinical recovery results from brisk sprouting of new motor axons from the nerve terminal with reinnervation of denervated muscle fibers.

B. Infant botulism is probably the most frequent form of botulism. The infant ingests the spores of *C. botulinum*, which lodge in the intestinal tract, germinate there, and produce botulinum toxin in the gut. Honey has often been implicated as the contaminated food in the infant disease. In adults, the small amount of *C. botulinum* in honey appears inadequate to colonize the GI tract. The typical presentation is an infant between the ages of 6 weeks and 6 months of age who exhibits generalized weakness and constipation. The weakness may start in the cranial muscles and then descend, causing a weak suck, a poor cry, and reduced spontaneous movement. The cranial muscles are weak, with poor extraocular movements, reduced gag reflex, and drooling. Finding *C. botulinum* in feces validates the diagnosis. The toxin is usually not detectable in the serum. EMG studies can point to the diagnosis in 80% to 90% of cases. Infantile botulism can range from mild to severe. Management centers on observation and general support (including respiratory stability). The recovery is usually excellent and runs a course of several weeks to several months. For infant botulism, IV botulinum immune globulin (BIG) trials in California were completed in early 1997 demonstrating safety and efficacy of human-derived BIG and a reduced mean hospital stay from 5.5 to

2.5 weeks. BIG is FDA approved and is available from the California Department of Health Services. Antibiotic use is not recommended for infant botulism because cell death and lysis may result in the release of more toxin.

C. Wound botulism occurs when toxin is produced from *C. botulinum* infection of a wound. The symptoms are similar to those of classic botulism except that the onset may be delayed for up to 2 weeks after contamination of the wound. The diagnosis is supported by EMG studies, demonstration of toxin in the patient's blood, or finding the organism in the patient's wound. Wounds that lead to botulism include direct trauma, surgical wounds, and wounds associated with drug use (such as IV and intranasal cocaine). The use of local antibiotics such as penicillin G or metronidazole may be helpful in eradicating *C. botulinum* in wound botulism.

Recommended Readings

Benatar M, Rowland LP. The muddle of mycophenolate mofetil in myasthenia. *Neurology*. 2008;71:390–391.

Ibrahim H, Dimachkie MM, Shaibani A. A review: the use of rituximab in neuromuscular diseases. *J Clin Neuromuscul Dis*. 2010;12:91–102.

Keogh M, Sedehizadeh S, Maddison P. Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database Syst Rev*. 2011;(2):CD003279.

Pascuzzi RM. The edrophonium test. *Semin Neurol*. 2003;23(1):83–88.

Pascuzzi RM. Myasthenia Gravis Website Publication, www.myasthenia.org, Medications and Myasthenia Gravis. January 2007. Contains an up-to-date review of adverse drug effects in myasthenia gravis.

Pasnoor M, Wolfe GI, Nations S, et al. Clinical findings in MuSK-antibody positive myasthenia gravis: a U.S. experience. *Muscle Nerve*. 2010;41:370–374.

Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology*. 2008;71:400–406.

Spillane J, Beeson DJ, Kullmann DM. Myasthenia and related disorders of the neuromuscular junction. J Neurol *Neurosurg Psychiatry*. 2010;81:850–857.

Villar RG, Elliott SP, Davenport KM. Botulism: the many faces of botulinum toxin and its potential for bioterrorism. *Infect Dis Clin North Am*. 2006;20:313–327.

Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: a randomized controlled trial. *Neurology*. 2007;68:837–841.

CHAPTER

49 Therapy of Migraine, Cluster, and Tension Headaches

James R. Couch Jr. and John F. Rothrock

I. MIGRAINE THERAPY

A. Theoretical considerations for migraine therapy. Most current theories of migraine relate in some way to the concept of neurovascular inflammation occuring within the distribution of the trigeminal nerve (ophthalmic division) or upper cervical sensory nerve roots. In brief, in response to various stimuli trigeminal nerve endings release neuropeptides (including calcitonin G-related peptide and substance P), which produce vasodilatation, increased vascular permeability, and extravasation of plasma proteins that in turn stimulate head pain receptors located on dural-based vessels. The resulting pain signal is transmitted via the trigeminal nerve to the trigeminal nucleus caudalis (TNC), thalamus, and, ultimately, to the cortex. Modulation of this signal presumably can occur at each of the involved synapses, and biologic sensitization of the head pain pathway proceeds sequentially from peripheral to central neurons. Cortical spreading depression (CSD) is postulated to initiate the neurovascular process occuring within the meninges and may also promote other biologic and clinical events related to migraine.

The trigeminovascular nerve endings possess presynaptic serotonin (5HT) 1-D receptors which can inhibit neuropeptide release and thus modulate the neurovascular response and peripheral transmission of pain signal. Presynaptic 5HT-1-D receptors also exist on serotoninergic connections to central neurons and may modulate central pain transmission.

Of note, the central dopaminergic system appears to facilitate migraine development. To oversimplify, it appears that serotonin 1-B and 1-D agonists ameliorate migraine, whereas dopamine agonists exacerbate the process.

B. Clinical considerations for therapy for headache. The most important aspects of headache treatment are: (1) correct diagnosis, (2) knowledge of the available options for treatment, both pharmacologic and nonpharmacologic, (3) selection of the treatment option most appropriate to the needs of a given patient, (4) educating the patient in the basics of his/her disorder and the treatment plan, and (5) commitment to ongoing management of the patient. The primary headaches are typically recurrent or chronic, and the patient typically will require continued attention and follow-up over variable periods of time. For the migraine patient, having a compassionate, interested physician is an asset of particular value.

Optimal therapy requires adequate data upon which to base management decisions. The most relevant clinical parameters to be considered are headache frequency, duration, and intensity, as well as symptoms associated with the headache. The success of therapy may be measured in any number of ways, but the first three parameters cited are paramount. The functional disability produced by headache is a variable that can be easily understood by the patient and can be measured as **disabling**—the patient is in bed or otherwise inactive >90% of the headache period, **severe**—usual activity is diminished by 50% to 90%, **moderate to mild**—more than 50% of usual activity is possible. Having patients keep a simple diary of their headache occurrences, their severity/functional disability, and any medication taken for the headache can significantly assist in directing management. Figure 49.1 provides an example of such a diary.

C. Algorithm for approach to the treatment of a patient with migraine (Fig. 49.2). Migraine is a clinical diagnosis—not one established by specific laboratory or radiologic tests—and thus should be considered a diagnosis of exclusion. The *International Classification of Headache Disorders* version 2 outlines the currently accepted clinical criteria for the diagnosis of migraine and other headache disorders.

Neurologic Services Headache Calender

Month:_____ Yr:_____

Patient Name:

_____

Headache Description:

I. Mild/moderate: Headache is present but does not limit activity, or activity is more than 50% or normal.

II. Severe: Can carry on some activity but overall activity is less than 50% of normal.

III. Disabling: Must go to bed.

Instructions:

1. Fill in the month and all the dates.

2. If headaches occur, write down the type of headache (I, II, or III) and any pain relief medications you take.

3. Bring your calender(s) to each clinic appointment - IMPORTANT!

Notes:

_____

_____

_____

Sun ____	Mon ____	Tue ____	Wed ____	Thur ____	Fri ____	Sat ____
Sun ____	Mon ____	Tue ____	Wed ____	Thur ____	Fri ____	Sat ____
Sun ____	Mon ____	Tue ____	Wed ____	Thur ____	Fri ____	Sat ____
Sun ____	Mon ____	Tue ____	Wed ____	Thur ____	Fri ____	Sat ____
Sun ____	Mon ____	Tue ____	Wed ____	Thur ____	Fri ____	Sat ____

FIGURE 49.1 Example of a calendar for recording headache with intensity indicated by amount of temporary disability related to the headache.

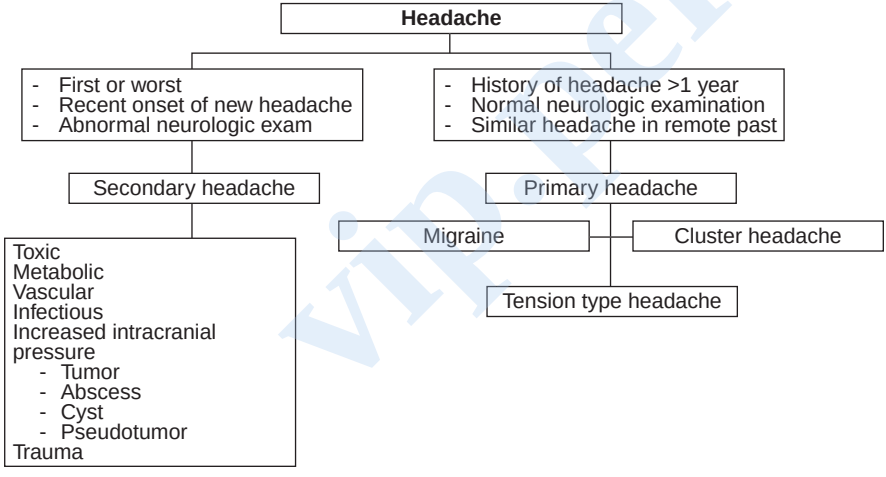

FIGURE 49.2 Algorithm for approach to the treatment of a patient with headache.

Table 49.1 outlines the process of developing a headache profile. This profile, by enabling the physician to compare the patient's headaches with established headache profiles, can be useful in establishing the diagnosis and developing an approach to treatment.

D. Migraine therapy.

1. Therapies for migraine can be divided into *symptomatic* and *prophylactic* (preventive). Symptomatic management can be further subdivided into nonspecific therapies and

TABLE 49.1 Key Features of a Headache Profile (Complete a Profile for Each Type of Headache)

Frequency of headache in terms of number per week, month, year, or even day
Duration of headache in terms of minutes, hours, or days
Intensity of headache, as measured by degree of temporary disability
Mild: does not interfere with activity
Moderate: interferes with activity to some extent but >50% of usual activity is possible
Severe: some activity is possible but < 50% of activity is carried out
Disabling: patient must go to bed with the headache
Symptoms associated with headache
General symptoms: photophobia, phonophobia, and osmophobia
Gastrointestinal and other autonomic symptoms
Neurologic symptoms (visual, sensory, motor, and speech)
Mood changes (depression, euphoria, and dysphoria)
Other symptoms
Precipitating factors for headache
Exogenous: exposure to odors, foods, weather changes, etc.
Endogenous: relation to menstrual cycle, sleep, stress, etc.
Age at onset of headache and course over time
Family history of headache
Psychological: presence of depression, anxiety, bipolar disease, and obsessive–compulsive disorder

(relatively) specific abortive therapies. An algorithm for migraine therapy is presented in Figure 49.3.

Symptomatic therapies for migraine are intended primarily for acute relief of pain. Although pain is the symptom that typically leads migraineurs to seek medical attention, migraine-associated nausea and vomiting, photophobia, phonophobia, kinesiophobia (worsening of the headache with activity), and aura frequently contribute to the patient's disability, apprehension, or both. In particular, antinauseants—some of which are effective for reducing migraine pain as well—often are a necessary component of a successful migraine treatment regimen.

Although monotherapy is ideal, the dynamic and typically nonstereotyped nature of the migraine process often requires use of two or more agents that are effective at different points in that process

2. **Nonspecific symptomatic therapy.**
   a. **Analgesics.** The simplest therapy for acute migraine is a nonsteroidal anti-inflammatory drug (NSAID) such as aspirin, ibuprofen, or naproxen sodium, all available as over-the-counter preparations and all effective for a many patients; larger dosages (e.g., 975 mg of aspirin, 800 mg of ibuprofen, or 550–825 mg of naproxen sodium) may be required. Addition of an antinauseant such as promethazine or hydroxyzine (25 to 50 mg) may be helpful in relieving both gastrointestinal symptoms and migraine pain.

      Acetaminophen (APAP) is an analgesic that lacks anti-inflammatory action. Some patients find 650 to 975 mg of APAP to be effective for early/mild migraine headache.

      The next step would be to try a more migraine-specific abortive drug (see **I.D.3.**). If this is not effective, then judicious use of a short-acting opiate/opioid can be considered.
   b. **"Narcotics" (opiates/opioids).**
      (1) **Self-administered narcotics.** These include codeine (30 to 60 mg), hydrocodone (5 to 10 mg), and oxycodone (5 to 10 mg). All can relieve pain but may not affect other migraine symptoms. Use of promethazine or hydroxyzine with the narcotic extends the analgesic effect of the narcotic and helps relieve gastrointestinal symptoms induced by migraine or the narcotic itself.
      (2) **Narcotic agonists–antagonists.** Butorphanol, a prototypic narcotic agonist–antagonist, commonly prescribes for migraine "rescue" is available as a nasal

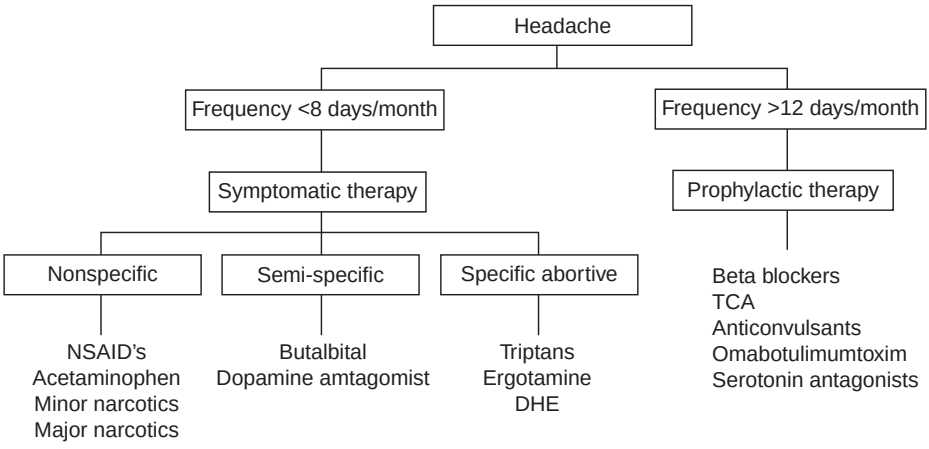

FIGURE 49.3 Use of symptomatic and prophylactic therapy for headache.

spray that delivers 70% of the potency of intramuscular (IM) injection at 1 mg per "puff." Use of 2 to 4 mg by nasal spray may produce significant pain control and prevent a trip to the emergency room. If intranasally administered butorphanol fails, injection of 2 to 4 mg of butorphanol or 10 to 20 mg of nalbuphine can be considered. These drugs stimulate opiate receptors at low doses but also act as narcotic antagonists and can elicit withdrawal symptoms at higher doses. Although these drugs have a lower habituating potential because they are κ receptor agonists, habituation can occur. The major side effects are dysphoria and hallucinations in addition to sedation. They cannot be used with any other narcotic because this may produce antagonism and narcotic withdrawal syndrome.

(3) **Clinician-administered narcotics.** If the above treatmenmts are ineffective, use of a narcotic such as meperidine (50 to 150 mg) or morphine (5 to 15 mg) may be indicated. These agents usually are given intramuscularly but can be given intravenously (IV) at lower dosages. Promethazine or hydroxyzine at 25 to 75 mg usually is quite effective as an adjuvant agent when given with a narcotic. Generally speaking, whether administreted by patient or healthcare provider (HCP), the use of narcotics should be limited to patients who have only occasional severe headaches that are refractory to other nonspecific analgesic approaches or to the relatively specific abortive therapies discussed in **I.D.3.**

3. **"Specific" symptomatic (abortive) therapies for migraine.** These medications appear to provide an antinociceptive effect for migraine headache but not for pain located elsewhere in the body. Response to these agents, however, is not diagnostic of migraine; serotonin 5HT-1-B and 1-D receptor agonists such as the triptans and dihydroergotamine (DHE) may produce temporary relief of headache due to underlying conditions as diverse (and serious) as subarachnoid hemorrhage or infectious meningitis.

a. **Ergotamine,** Isolated from the rye fungus in 1925, ergotamine was the first abortive medication intended for migraine. It stimulates most of the aminergic receptors and consequently has many pharmacologic actions. It stimulates the 5HT-1-B and 1-D receptors as avidly as does sumatriptan.

Ergotamine can cause coronary vasoconstriction, and there have been several reports of myocardial infarction associated with ergotamine use. It also can cause vasoconstriction in the digits; this typically is of no clinical significance, but with long-term use of ergotamine peripheral cyanosis, acroparesthesias, and peripheral neuropathy may result. It remains unclear whether these findings are related to microvascular constriction, including constriction of vasa nervorum, or whether ergotamine has a separate and direct neurotoxic effect.

Frequent administration of ergotamine may result in medication overuse headache (MOH). The consensus is that ongoing use of ergotamine more than 10 days per month can produce MOH.

Because of ergotamine's side effects and potential toxic effects, and because the triptans are equally if not more effective, ergotamine now is prescribed infrequently.

b. **Triptans.** This is a relatively new class of medications synthesized specifically for the treatment of migraine. Investigations of **serotonin** have identified four classes of receptors: **5HT-1** (presynaptic), **5HT-2** (postsynaptic), **5HT-3** (related to the g-protein system), and **5HT-4** (related to transporter function). The triptans are 5HT-1-B, 1-D receptor agonists (with lesser effects on the 5HT-1-A and 1-F receptors). These medications have been found to be remarkably effective for the symptomatic relief of migraine.

(1) **Mechanism of action.** Peripherally via their action on the 5HT-1-B receptor, triptans constrict the intracranial arteries. This activity is highly cerebroselective, but the drugs do exert some relatively minimal coronary vasoconstrictive effect (see **I.D.3.b(3)**).

In the peripheral nervous system, 5HT-1-D receptors reside at the presynaptic terminals of nerves (chiefly the ophthalmic branch of the trigeminal) which supply head pain receptors located on dural-based blood vessels. Stimulation of these 5HT-1-D receptors inhibits the nerve's release of neuropeptides, which—otherwise left unchecked—would provoke the relevant blood vessel to leak proteins that produce so-called neurovascular inflammation. The resulting inflammation in turn can further sensitize trigeminal nerve endings and reinforce transmission of head pain signal.

In the CNS, the 5HT-1-D receptor is present on neurons within the TNC, as well as the locus ceruleus, dorsal raphe nucleus, and other brainstem structures. Some triptans (rizatriptan, zolmitriptan, and naratriptan) are CNS penetrant, whereas sumatriptan and ergot derivatives are less able to cross the blood–brain barrier in its normal state. Because all triptans have similar CNS side effects, however, it is postulated that during migraine attacks the blood–brain barrier opens, and drugs with lower lipophilicity and thus typically less CNS penetration can enter the CNS during the attack.

Whether the major effect of the triptans in stopping migraine is **peripheral** (through 5HT-1-D receptors at the trigeminovascular junction within the meninges) or **central** (through antinociceptive 5HT-1-D receptors located on CNS neurons) continues to be a matter of debate. Perhaps the triptans' antimigraine effect requires both.

(2) **Clinical trials.** The first clinical trials involved sumatriptan, and the methodology developed for those trials has set the standard for all subsequent trials involving symptomatic antimigraine therapy. Understanding how the trials were conducted may serve to help understand the drugs, their use, and their limitations. A brief summary is given below.

(a) The chief outcome variables assessed were level of pain intensity and presence versus absence of nausea, vomiting, photophobia, and phonophobia.

i. Pain was reported as none, mild, moderate, or severe by the patient's own internal standard.

ii. Subjects were instructed to administer the study drug only when their acute head pain became moderate or severe.

iii. The primary criterion of success was pain reduction from moderate/severe at the time of drug administration to mild or none (relief), or none (pain-free) at 2 hours (see Fig. 49.4).

Secondary measures included the following: remission of baseline nausea, photophobia, or phonophobia at 2 hours; recurrence of moderate or severe headache within 24 hours; sustained pain-free at 24 hours; and change in headache-related disability at 2 and 24 hours after administration. Table 49.2 lists the seven triptans and the sumatriptan/NSAID compound currently available. In clinical trials, those oral triptans with longer half-lives (frovatriptan and naratriptan) have been associated with a somewhat lower response rate at 2 hours and a lower incidence of early recurrent headache

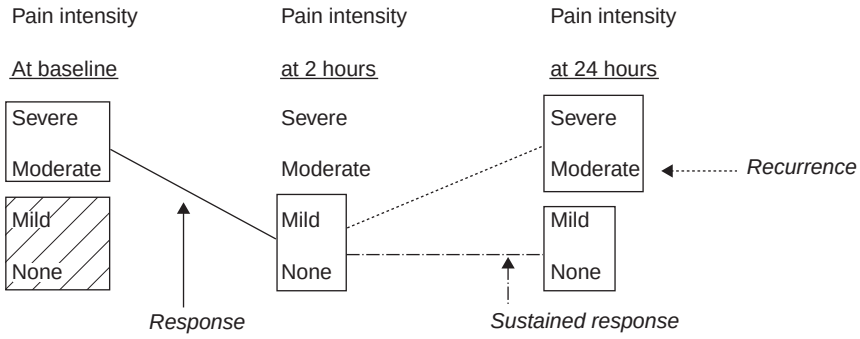

FIGURE 49.4 Method for trials of headache therapy since 1988. At baseline, pain is measured as severe, moderate, mild, or none and measured with the same scale at times up to 24 hours. Initial medication is taken only when pain is severe or moderate. The terms *response, recurrence,* or *sustained response* are defined diagrammatically.

than the "fast-acting" oral triptans. The triptan formulation with the shortest half-life and T_{max}—subcutaneously administered sumatriptan—is the most likely to produce headache relife at 1 and 2 hours but also is associated with a relatively high incidence of early recurrent headache.

Which oral triptan is "best?" Head to head studies involving "active comparators" (i.e., triptan vs triptan) have done little to provide an answer, if one exists. Treximet, the oral compound containing sumatriptan (as Imitrex RT) and naproxen sodium was demonstrably superior to oral sumatriptan, but that drug's effect relative to its components administered simultaneously but independently or to others of the oral triptan class is unknown. From a clinical standpoint, however, there appears to be significant idiosyncrasy in the response of migraine patients to triptan therapy. A tripans that significantly benefits one patient may be completely ineffective for the next (and vice versa), and in the individual patient the failure to respond to one triptan does not necessarily predict failure to respond to others within the class. The cause(s) underlying these idiosyncrasies remain unclear

(3) **Adverse effects.** The most common adverse effects of the triptans include somnolence, fatigue, asthenia, nausea, and dizziness. Chest discomfort (typically described as "pressure") or a sensation of neck "squeezing" occur in a significant number of patients. The chest symptoms are thought to be related to stimulation of esophageal receptors with consequent esophageal spasm, but at times prudence dictates that a cardiac origin be excluded.

The **major, clinically significant** adverse events related to triptan therapy involve the heart. There are 5HT-1-B receptors on the coronary arteries, and both *in vitro* and *in vivo* studies have indicated that administration of a triptan potentially can cause as much as a 20% reduction in the diameter of coronary arteries. If the patient has a significantly stenotic atherosclerotic coronary lesion, then, this 20% constriction theoretically could be sufficient to occlude the vessel. There have been myocardial infarctions reported to occur in close temporal association with administration of triptans and also with ergotamine and DHE. Patients at risk for asymptomatic coronary disease should be screened appropriately before using triptans, ergotamines, or DHE. **Patients with known cardiac disease should not take triptans.**

As with their therapeutic effect, the triptans' adverse event profile is relatively idiosyncratic. Tolerance to triptan therapy varies widely amongst migraineurs, and if a given patient has prominent side effects with use of one triptan, this does not necessarily guarantee that the patient will have the same experience with another.

Overuse of triptans can produce MOH. Triptan usage should be limited to not more than 3 days per week, 10 days per month and, generally, not more than 2 doses within a 24 hour period.

TABLE 49.2 Currently Available Triptans: Usual Dose

Drug and Route	Marketed Formulations (mg)	Usual Dose (mg)
Oral		
Sumatriptan	25, 50, 100	100
Zolmitriptan (tablet and "melt")	2.5, 5	5
Rizatriptan (tablet and "melt")	5, 10	10[a]
Almotriptan	12.5	12.5
Eletriptan[a]	20, 40	40
Naratriptan	1, 2.5	2.5
Frovatriptan	2.5	2.5
Treximet[b]	85/500	85/500
Nasal Spray		
Sumatriptan	5, 20	20
Zolmitriptan	5	5
SC		
Sumatriptan	4, 6	6

[a]5 mg dose (tablet formulation only) typically prescribed to patients also taking propranolol: drug–drug interaction decreases rizatriptan metabolism and so increases plasma concentration.
[b]Compound containing sumatriptan (as Imitrex RT 85 mg) and naproxen sodium (500 mg).

(4) **Administration.** Table 49.2 lists the formulations and typical doses of the triptans currently available. Sumatriptan has the widest range of formulations (oral tablet, nasal spray, and subcutaneous (SC) injection), but for all the triptans the vast majority of patients utilize oral preparations. The benefits of oral administration must be weighed against the fact that many patients find such therapy to be inconsistently useful for migraine headache of moderate-to-severe intensity and typically much more effective if employed earlier in the attack, when pain is mild to moderate.

The rapidly melting tablet formulations of rizatriptan and zolmitriptan have achieved good acceptance owing to their convenience; they are no more effective—or rapidly effective—than the conventional tablet formulations of those drugs. Sumatriptan or zolmitriptan nasal spray can be used when the patient is too nauseated to take medication orally and disinclined to self-inject. The response time for zolmitriptan nasal spray is modestly faster than that of its oral counterpart, and that of sumatriptan nasal spray is roughly equivalent to the tablet.

Of the triptans, subcutaneously administered sumatriptan (4 mg or 6 mg per dose) has the fastest onset of effect, with headache relief occurring as early as 10 to 20 minutes following administration. About 70% to 75% of patients experience relief within 1 hour. For patients who awaken with their headache already severe or those who experience very rapid onset and escalation of headache, this is a very useful preparation.

c. **DHE.** Dihydroergotamine mesylate (DHE or DHE 45) is an agonist for most aminergic receptors, including the 5HT-1, 5HT-2, catecholamine, and dopamine receptors. Experimentally, it is equipotent to sumatriptan as a 5HT-1-B, 1-D agonist. DHE may be given IV, IM, or as a nasal spray. The compound is chemically unstable when exposed to air or light and must be kept refrigerated and in the dark.

Given IV, 1 mg of DHE is as potent as SC sumatriptan for migraine relief. Given IV, DHE can produce relief from migraine within 15 to 30 minutes and works well in up to 80% of migraine patients. The drug is miscible with prochlorperazine, and the addition of 5 mg of the latter may help offset migraine (or DHE) induced nausea as well as work synergistically with DHE to treat the headache itself (see I.D.3.e). IV DHE is quite appropriate for use in the emergency room for treatment of severe migraine, and the drug is also useful in treating patients hospitalized for status migrainosus or withdrawal from symptomatic medication that has been causing MOH. Table 49.3 outlines the in-patient protocol introduced by Raskin. If a patient does not respond to the first two or three doses of DHE, however, other therapeutic approaches should be considered.

TABLE 49.3 DHE: Dosing

IV use (Raskin protocol):
Metoclopramide 10 mg (IV over 1 min) or prochlorperazine (5 mg IV push with DHE)
For metoclopramide, wait 5 min to allow distribution
DHE 0.5 mg IV over the course of 60
Wait 10–15 min; if no headache relief and no significant increase in nausea or other adverse event, repeat DHE 0.5 mg IV; if relief following second dose, begin with DHE 1 mg for subsequent treatments
Ongoing: may repeat above every 8 hr for up to 4–6 d
Side effects: nausea, chest pressure, anxiety
SC or IM: use 1 mg with or without antiemetic

In patients believed to be at potential risk, evaluate for coronary disease before use of DHE. Do not use for patients at risk of myocardial infarction or stroke.

DHE has a half-life of 10 hours. With repeated dosing, accumulation of metabolites over time can produce side effects of irritability, sedation, peripheral edema, and vasoconstriction. Whereas ergotamine has a greater effect on arterioles, DHE is primarily a venoconstrictor. The side effects of DHE are similar to those of ergotamine but less intense, and the incidence of peripheral and coronary vasospasm is much lower with DHE than with ergotamine.

DHE also can be used as a 1 mg IM or SC injection. Studies have shown a slower onset of action and a 60% to 70% rate of headache relief at 2 hours. Patients may be trained to self-inject. DHE administered via nasal spray is decidedly less effective than when the drug is administered via the IV, IM, or SC routes.

d. **Isometheptene "plus".** These compounds are usually a combination of isometheptene mucate (a weak catecholamine agonist) 65 mg, dichloralphenazone (an antihistamine) 100 mg, and APAP 325 mg. The compound's receptor profile has not been studied, but it appears to have a modestly positive effect in treating acute migraine action. The typical dosing regimen has been one or two taken orally at headache onset, repeated at hourly intervals (up to six total doses per day). Manufacturing of this compound virtually has ceased, and it is now consequently difficult for patients to procure the drug.

e. **Dopamine antagonists.** An antiemetic such as metoclopramide (10 mg), prochlorperazine (5 to 10 mg), chlorpromazine (10 to 25 mg), or droperidol (2.75 mg) given IM or IV can be tremendously helpful in relieving persistent, severe migraine headache. These drugs also may be helpful when self administered orally or rectally. Hypotension, acute dystonic reactions, and akathisia can occur with any of these agents. So effective are these drugs that a dopamine antagonist typically should be considered before parenteral administration of a narcotic.

4. **Preventive antimigraine therapy (PAMT).** The ideal outcome from preventive therapy for migraine is to render the patient headache-free or nearly so at the cost of no or minimal side effects. A less desirable but often more realistic goal is simply to provide for the patient some clinically meaningful reduction in the frequency and severity of his/her migraine attacks.

How therapies prescribed for migraine prophylaxis may achieve that result remains speculative. If, as with primary epilepsy, migraine reflects a genetically "hypersensitive" brain, then presumably an effective prophylactic therapy has served in some way to diminish neuronal hypersensitivity. The specifics of how such "desensitization" is accomplished are unknown. It has been suggested that stimulation of the 5HT-2 receptor is related to the migraine-preventive effect. More recent work has shown that some of the most clinically effective PAMT agents inhibit CSD and by this mechanism suppress migraine. Further research is needed.

a. **General principles of preventive therapy.** The decision whether to use preventive medication is based on the following factors: (1) frequency of migraine, (2) intensity of migraine, (3) duration of headache, (4) how well the migraine patient's attacks are

responding to any symptomatic medication(s) prescrided, (5) the patient's willingness or desire to try the prophylactic approach, and (6) side effects of therapy. Occurrence of three or four headache attacks per month or more than 8 days of headache per month are reasonable thresholds for the consideration of prophylactic therapy.

It is not uncommon for patients to experience significant side effects from PAMT, and for each patient, the therapeutic benefit must be balanced against the extent of side effects.

The drugs for which class I data for migraine prevention exists are methysergide (not currently available in the United States), certain *ß*-adrenergic blocking agents (propranolol and timolol); amitriptyline; valproic acid (VPA); topiramate and onabotulinumtoxinA (onabotA—indicated for chronic migraine (CM) only). Other drugs commonly used for PAMT but possessing less of a scientific basis for that use include other antiepileptic drugs (e.g., gabapentin, levitiracetam, and pregabalin), other beta blockers (e.g., nadolol and metoprolol), other tricyclics (e.g., nortriptyline and protriptyline), calcium antagonists (e.g., verapamil), and tizanidine.

Many of these preventive medications have numerous side effects and may not be well-tolerated. The usual procedure with such medications is to start with a low dose and advance the dose sequentially until either a positive therapeutic effect is observed or limiting side effects occur. Monotherapy should be attempted before combinations of prophylactic medications are tried. Typically effective daily dose ranges for the most commonly used PAMTs are presented in Table 49.4.

b. **ß-blocking agents.** Propranolol, approved by the FDA for migraine prophylaxis in 1974, is discussed as the prototype of this group.

The pharmacology of propranolol is complex. As a nonspecific *ß*-adrenergic blocking agent, it has many clinical effects, including reduction of blood pressure, heart rate, and cardiac contraction; inhibition of bronchodilation; and decrease in the gluconeogenic response among diabetic patients taking insulin. In small doses, propranolol has also an antianxiety effect.

The *ß*-adrenergic blocking agents without intrinsic sympathomimetic activity (ISA) appear to have a preventive antimigraine effect, whereas those with ISA appear to have minimal effect on migraine.

The **side effects** of propranolol include fatigue or a lack of energy, sedation, and weight gain. Orthostatic hypotension and syncope can occur if the hypotensive effect is too great. Because (inhibitor) effect on bronchodilation, propranolol should not be used in individuals with asthma.

TABLE 49.4 Commonly Prescribed Prophylactic Antimigraine Agents

	Usual Effective	Daily Dose (mg)
ß-adrenergic blocking agents		
Nonspecific ß-blockers	Propranolol	80–240
	Nadolol	20–40
	Timolol	20–30
Specific $ß_1$ blocking agents	Atenolol	25–100
	Metoprolol	50–100
TCAs	Amitriptyline	25–150
	Doxepin	25–150
	Nortriptyline	25–150
	Imipramine	75–150
"Antiepileptic" medications		
	Topiramate	100
	Valproate*	1,000
	Gabapentin	600–2,700
	Zonisamide	100–300
Calcium channel blockers	Verapamil	120–240
NSAIDS	Naproxen sodium	1,100

* Given as an "ER" (extended release) formulation.

Because of the drug's negative chronotropic and inotropic effects, patients may find their capacity for exercise diminished.

The dose of propranolol for migraine prophylaxis can vary from as little as 20 to 30 mg per day to as much as 360 mg per day. In most patients destined to respond to propranolol, doses of 80 to 240 mg per day are effective. The dose–response relationship appears to be quite idiosyncratic. As with many other PAMTs, the typical means of initiating treatment with propranolol is to begin with a relatively low dose (e.g., 20 mg twice daily) and then increase as needed/tolerated.

Three contraindications should be noted: (1) propranolol should not be given to patients with diabetes, because it masks the response to hypoglycemia, (2) propranolol can precipitate asthmatic reactions in patients with actual or latent asthma, and (3) propranolol can enhance or precipitate depression, and this effect may be pronounced.

Other *ß*-blocking agents without ISA may be effective as is propranolol, but none has been tested for that indication as thoroughly for migraine prophylaxis. Although some of these agents may have desirable properties such as longer half-life, there has been very little evidence that use of one *ß*-blocking agent without ISA is better than any other. Typically, if one *ß*-blocking agent fails, better results are seldom obtained with trials of other *ß*-blockers.

c. **Tricyclic antidepressants (TCAs)** Whereas the ß -adrenergic blocking agents typically have been more effective for "pure" episodic migraine, the TCAs generally have been favored for so-called mixed headache (i.e., what was felt in the past to represent co-existing chronic tension-type headache and episodic migraine). Amitriptyline is the only TCA for which class I data exist. Other TCAs commonly used for migraine prophylaxis are listed in Table 49.4.

The **pharmacologic properties** of TCAs are complex. These agents inhibit reuptake of serotonin and norepinephrine at nerve endings and have anticholinergic and *ß*-adrenergic blocking effects.

For amitriptyline, a starting dosage of 10 to 25 mg at bedtime usually is tolerated. The dosage may be increased 10 to 25 mg every 1 to 2 weeks to a maximum of 150 mg per day. As with propranolol, the response to TCAs is idiosyncratic and not clearly related to dose or blood levels. If the patient has no side effects and no relief, continue to increase the dose. Giving the entire dose at bedtime may work well for most patients, but some experience recurrence of headache in the afternoon or evening with this regimen.

The typical side effects of the TCAs are linked to the class's anticholinergic effect; they include drowsiness, dry mouth, constipation, impaired urination, blurred vision, and weight gain. Some patients accommodate to the drug with slow dose escalation or temporary dose reduction. Anxiety and paradoxical stimulation with insomnia may occur. Amitriptyline has been associated with cardiac arrhythmias and in rare cases with sudden death.

Combinations of amitriptyline in doses of 75 to 150 mg per day and propranolol at 80 to 160 mg per day have been used by some headache subspecialists to manage migraine, and selected patients appear to experience a significant synergistic effect.

d. **Valproic Acid** (VPA) It is approved by the FDA for migraine prophylaxis. The formulation divalproex sodium is better tolerated than VPA, per se (especially in terms of nausea and gastric irritation). The major side effects of divalproex sodium are weight gain, tremor, and hair loss. These remit when the drug is discontinued. Sedation and cognitive impairment occasionally may occur.

Special considerations for women include an increased incidence of polycystic ovary syndrome and potential fetal harm (increased risk of neural tube closure defects). Categorized as class D, VPA should be used only when there is no risk of pregnancy. Women on the drug should receive folic acid supplementation (1 mg per day) to diminish risk to the fetus from an unexpected pregnancy.

Alterations of liver function by changes in carnitine metabolism occur and can result in an elevated level of ammonia in the blood. Clinically significant hepatotoxicity is largely restricted to children under 2 years of age but has been reported (albeit quite rarely) in adults.

e. **Topiramate.**

Topiramate, approved for anticonvulsant therapy in 1996, was first tested as a PAMT in the late 1990s and after several large trials confirming its effectiveness was approved by the FDA for PAMT in 2004. It has a number of pharmacologic effects including inhibition of carbonic anhydrase and alteration of the sodium channel by alteration of magnesium modulation. The drug also may produce acidosis of significant degree. The most common side effects are limb paresthesias, nausea, somnolence, and cognitive impairment (impaired recent memory, concentration, and word-finding). Altered taste (especially for carbonated beverages) is quite common as well, and anorexia may occur. Weight loss of up to 5% to 7% of body mass has been reported in some studies. Occasional subjects may experience dysphoria, anxiety, or depression.

For subjects prone to form renal calculi, topiramate can significantly increase the risk of calculus formation. There are rare reports of acute glaucoma associated with topiramate use, typically occurring within the first 2 months of treatment.

To maximize tolerability, one should start treatment with a dose of 25 mg nightly and increase by 25 mg per day each week to a target level of 50 mg twice daily. If the patient has experienced no clinical improvement after 6 to 8 weeks of treatment at that dose, it is unlikely topiramate ultimately will prove effective (even with upward dose adjustments); continuing treatment at that dose or increasing the dose typically will yield only side effects. On the other hand, those patients who initially experience a "partial positive response" at the 50 mg twice daily dose may improve further if treatment is continued at that dose or slowly advanced. Alternatively, some patients who improve on topiramate 50 mg twice daily but cannot tolerate that dose may continue to experience significant improvement in their migraine (and elimination of side effects) at a lower dose.

Like VPA, topiramate is contraindicated for use in pregnant females or females at the risk for pregnancy. Due to its clear association with cleft palate, it is a class D drug.

f. **OnabotulinumtoxinA (onabotA).**

OnabotA injection therapy was approved by the FDA for the treatment of CM in October 2010; it has not been found to be effective for use in episodic migraine (i.e., migraine with 15 days of headache monthly). Each treatment involves a total of 31 IM injections at seven fixed sites over the forehead, temples, occiput, neck, and trapezius muscles, and the total dose administered is 155 units. Injections are performed every 3 months until remission to infrequent episodic migraine has been attained.

The most common side effects associated with onabotA therapy for CM are neck pain or stiffness, muscle weakness (typically involving the neck: "wobbly neck"), and ptosis.

In one recent head-to-head trial involving onabotA versus topiramate for the suppression of CM, the two therapies were roughly equivalent in terms of efficacy, but patients preferred the former due to better tolerability.

g. **Other preventive antimigraine agents.** There are a number of other drugs that have received attention as potential PAMT, but some possesses sufficient class I data to support its use, and some has received FDA approval. These are summarized below.

(1) **Anticonvulsants.** Of the antiepileptic drugs not previously listed, gabapentin arguably possesses the most compelling evidence base for use as a PAMT (for both episodic migraine and CM). There have been multiple trials of the drug for migraine prophylaxis, and there are (limited) class I data to support its use, but it does not have FDA approval for this indication.

Gabapentin is excreted renally and thus will not interact adversely with drugs requiring hepatic metabolization. The most common side effects of gabapentin are "dizziness"/disequilibrium, sedation, irritability, depression, and cognitive impairment.

Levetiracetam, zonisamide, oxcarbazepine, and pregabalin all possess class II or III data suggesting potential utility for migraine prophylaxis, but thus far the evidence to support their use falls well below what exists for VPA, topiramate, Onabot A (for CM), and—to a lesser extent—gabapentin.

(2) **Newer antidepressant agents.** Of the newer antidepressants, trazodone and nefazodone may exert some antimigraine activity. The selective serotonin reuptake inhibitors (SSRIs) commonly have been used as PAMT, but the data from controlled studies investigating their utility have been negative. Although the "mixed" SSRI/norepinephrine reuptake inhibitors often are helpful in treating the depression and anxiety disorders that so often accompany migraine, there is little objective evidence to support their use as PAMTs.

(3) **Calcium channel blocking agents.** Although drugs from this class generally have been disappointing as PAMTs, there may exist a small subpopulation of migraine patients in whom certain calcium antagonists may be effective.

For PAMT, the prototype of this group is verapamil. When effective, it usually is at a dose of 120 to 240 mg per day. Although orthostatic presyncope may occur, the drug's most common side effect is constipation.

Flunarizine, a calcium channel blocking agent available in Europe, Canada, and Latin America, has class I data for effectiveness as a PAMT and is approved in those countries. The side effects of somnolence and weight gain have limited its use, however, and introduction into the United States seems unlikely.

(4) **Cyproheptadine.** Introduced in the 1960s, cyproheptadine is an antihistamine with a tricyclic structure. Controlled studies investigating its use as a PAMT did not show a statistically significant effect; despite this, cyproheptadine still is used as an agent for migraine prevention (especially in the pediatric population). The drug commonly causes sedation and weight gain.

II. CLUSTER HEADACHE THERAPY AND MANAGEMENT

A. Cluster is one of the most painful headaches. It is almost always unilateral and most prominent in or around the eye. Most patients experience rapid onset of pain over 5 to 15 minutes, a plateau of intense pain lasting 15 to 90 minutes, and then rapid resolution to no pain. It often occurs in cycles lasting 4 to 12 weeks, and during cycles discrete attacks may occur up to six times per day. Given the brevity of the individual attacks, symptomatic treatment rapidly must offer relief to be of any real help to the patient while an attack is ongoing.

B. Symptomatic therapy. As with migraine, therapy for cluster headache can be divided into symptomatic and prophylactic intervention, with the latter intended to terminate a cycle prematurely. Symptomatic treatment can be further subdivided into nonspecific analgesic medications and relatively specific abortive medications.

1. Nonspecific oral (narcotic or other analgesic) medication. Because of the typically brief duration of the cluster attack and the gastroparesis that accompanies the headache, these drugs generally are very ineffective in managing acute cluster headache.

2. Relatively specific abortive medications. These include SC, intranasal or oral sumatriptan and other triptans, DHE, ergotamine, and oxygen.

a. **Triptans.**

(1) **Sumatriptan** 4-6 mg subcutaneously injected typically produces rapid and consistent relief from cluster headache (usually within 10 minutes of administration). Unless a contraindication to its use exists, it should be considered first-line therapy for acute cluster headache. Studies of oral or nasal sumatriptan also have demonstrated some effectiveness, but the onset of relief usually is delayed for at least 30 minutes following administration.

(2) **Other triptans** have been used. Because of slow absorption, oral triptans have been relatively ineffective. Zolmitriptan nasal spray has been reported to be moderately effective and in selected cases may represent an acceptable alternative to injectable sumatriptan.

b. **DHE** 1 mg given as a SC or IM injection can produce adequate relief from acute cluster headache. Onset of action typically is within 5 to 10 minutes following administration.

c. **Ergotamine** for acute cluster headache can be administered orally or rectally. Studies by Kudrow have suggested that oral ergotamine can induce pain relief after approximately 10 minutes.

d. **Oxygen** delivered per rebreather mask at a rate of 8 to 10 L per minute can produce good relief from acute cluster headache within a few minutes of use. The patient typically must continue oxygen administration for 15 to 30 minutes, and in many cases, the headache will recur soon after the oxygen is discontinued.

C. Prophylactic therapy for cluster is intended (1) to terminate a cycle of cluster, (2) to prevent progression of cyclical cluster to the chronic variant (i.e., "secondary" chronic cluster), or (3) to suppress primary or secondary chronic cluster (i.e., cluster that is persistent/noncyclical but otherwise typical).

1. **Steroids.** Corticosteroids are highly effective in terminating a cycle of cluster. The most commonly used steroid preparation is prednisone, but equipotent dosages of other corticosteroid preparations appear to achieve the same degree of therapeutic success.

   The doses of prednisone reported to be effective in cluster headache vary from 10 to 100 mg per day, but typically a higher dose (i.e., 60 to 100 mg per day) is used to initiate steroid therapy. This dose usually is maintained for at least 5 to 7 days. If the cluster cycle ceases, the dose then is sequentially reduced and steroid therapy discontinued altogether after approximately 2 weeks. As the steroid dose is reduced, it is common for the cluster headaches to recur (especially below doses of (or equivalent to) 15 to 20 mg of prednisone per day). As a result, steroids usually are best used for achieving rapid termination of the cycle, with another preventative medication (typically verapamil—see II.C.3) added to help ensure the cycle does not recur as the steroid is discontinued. The duration of therapy with this second preventative drug is variable, but most often the drug is continued for the approximate duration of the patient's usual cluster cycle.

   Steroids may not be used for prolonged periods consequent to the risk without risk of significant side effects. Those side effects, well-known to physicians, include insomnia, increased appetite/weight gain, increased fragility of blood vessels and skin, diabetes, osteoporosis, aseptic necrosis of the head of the femur, obesity, myopathy, and emotional/behavioral instability (at times escalating to the level of psychosis).

2. **Methysergide** was the first medication to demonstrate a prophylactic effect among patients with cluster headache. This medication is no longer available in the United States but may be obtained in Canada. Doses of up to 8 mg per day may be used. The prescribing physician should be familiar with the drug's potential side effects (systemic fibrosis, in particular) Methylergonovine molecularly similar to methysergide, may represent an effective alternative.

3. **Calcium channel blocking agents.** Verapamil has been shown to have a prophylactic effect in cluster headache. Because of its relatively benign side effect profile and its effectiveness, it has become the preferred agent for cluster prophylaxis. Doses of verapamil for cluster treatment vary from 120 to 720 mg per day, as needed/tolerated. Side effects include bradycardia, hypotension, insomnia, and constipation. The results with verapamil are generally good if steroids initially have been used to halt the cycle; used by itself, only 50% to 60% of cycles are brought under control. There is a tendency for the drug's effectiveness to diminish in subsequent cycles of therapy. Verapamil should not be used in patients with sick sinus syndrome, atrioventricular block, or Wolff–Parkinson–White's syndrome.

4. **VPA and topiramate** have been reported to have a prophylactic effect in cluster, but the evidence to support their use is scant. These are alternatives to consider if verapamil fails.

5. **Combined therapy.** In the solid majority of cases a therapeutic approach combining an oral steroid and verapamil elicits an adequately positive response. At the same time oral steroid therapy is begun, the patient also starts taking verapamil (typical dose: 80 mg three times a day, increasing sequentially to 240 mg three times a day as needed/tolerated). If this approach is unsuccessful (and in contrast to migraine, wherein prophylactic monotherapy is preferred), an additional prophylactic agent may be added; VPA, topiramate, or methylergonovine are arguably the best options. In addition, occipital nerve blocks may be remarkably helpful in suppressing or terminating a cluster cycle.

   Many medications commonly prescribed for the prevention of migraine headache are relatively ineffective in treating cluster (e.g., β-adrenergic blocking agents and TCAs). Little information presently exists regarding the utility of onabotA injection therapy for cluster.

III. CHRONIC CLUSTER HEADACHE

A. Medications. Chronic cluster headache is notoriously difficult to manage effectively. "Chronic cluster" implies the patient is experiencing typical cluster attacks, but the cycle has persisted for more than 6 months without remission. Lithium has been reported to be effective in treating chronic cluster; the typical dose is 600 to 1,200 mg per day (to maintain the blood level at 0.6 to 1.2 mEq per L). Signs and symptoms of lithium toxicity include confusion, disorientation, drowsiness, seizures, thirst, and rash; significant action tremor may develop even when dose and blood level are relatively low.

In some cases ongoing treatment with verapamil, methergine, or both is sufficient to suppress chronic cluster. As with the more common cyclical variant, occipital nerve blocks may afford some benefit, but the utility of onabotA for chronic cluster has not been established.

B. Surgical therapy.

1. **Trigeminal nerve procedures.** For some patients with prolonged and otherwise treatment-refractory chronic cluster, surgery on the trigeminal nerve has proven to be at least somewhat effective. Two procedures have been advocated—trigeminal gangliotomy by radiofrequency lesioning and preganglionic nerve root sectioning. Both produce diminished sensation in the distribution of the trigeminal nerve, and patients who have undergone these procedures often find that they still have "shadow" sensations similar to their previous cluster attacks but absent the severe pain. To date, no serious complications have occurred in the small series that have been reported. We presently lack long-term follow-up data to indicate whether or not these procedures will produce indefinitely sustained relief.
2. **Deep brain stimulation** (DBS) has been evaluated as an intervention for very severe and treatment-refractory chronic cluster headache in several small series. The reported results suggested benefit, but serious adverse events occurred in some subjects. This is still considered an experimental procedure.
3. **Occipital nerve stimulation** (ONS). ONS via surgically implanted stimulators was been evaluated as a therapy for otherwise treatment-refractors chromic cluster and early results have been encouraging. As with DBS, this intervention should be considered experimentally.

IV. EPISODIC TENSION-TYPE HEADACHE

For acute episodic tension-type headache (ETTH), use of a "simple" analgesic or NSAID such as ibuprofen, naproxen, or APAP usually suffices. For more intense ETTH, a combination of butalbital, caffeine and aspirin, or APAP may be helpful. At times, addition of a muscle relaxant in a low dosage (e.g., diazepam 2 mg or orphenadrine 50 mg) can prove beneficial. Very often, however, the individual with pure ETTH does not bother to see a physician for evaluation and treatment and does so only if the tension headache becomes atypically severe or clearly has developed into migraine.

Chronic prescription of butalbital compounds or benzodiazepines always should be undertaken with care. These drugs are potentially habituating and lend easily to overuse.

V. CHRONIC DAILY HEADACHE

A. Chronic daily headache (CDH). CDH is exceedingly common, afflicting over 4% of the general population. Most CDH is due to chronic tension type headache (CTTH) or CM; other primary headache disorders causing CDH (e.gg, hemicrania continua and new daily persistent headache) are relatively rare. CM frequently is misdiagnosed as so-called mixed headache or attributed to sinus disease or another extrinsic factor. According to the ICDH 2 classification system, CM implies an established history of migraine and 15 or more days of headache monthly for at least 3 consecutive months with at least 8 of those days involving "typical" migraine or headache responsive to treatment with a triptan or an ergotamine. As with ETTH, individuals with CTTH are less likely to seek medical attention; the overwhelming majority of CDH patients presenting to a headache subspecialty clinic have CM.

B. MOH. Popularly known as "rebound headache" MOM is an entity that most often occurs in conjunction with and complicating CM. The MOH syndrome develops from overuse of symptomatic medications, whereas MOH may develop fairly rapidly when the offending drug is a triptan or ergotamine (and remit no less rapidly following withdrawal or partial withdrawal from the drug), with virtually all of the other symptomatic medications for acute migraine-prescription or over-the-counter-months of overuse typically are required to develop MOH (and clinical improvement following withdrawal may not occur for months).

MOH is frequently insidious in its onset. Over time, a patient may find that the overused symptomatic medication becomes progressively less effective as an abortive agent even when higher doses are used, and as he/she consequently administers an ever-increasing quantity of the drug, the associated CM grows ever more pervasive. The diagnosis of MOH can be confirmed only in retrospective, by discontinuing the overused drug(s) and demonstrating that the headache disorder improves over the next 3 to 6 months. Although exceptions apparently exist (e.gg, topiramate and onabotA), overuse of symptomatic medication is widely believed to inhisit the ameliorative effect of whatever prophylactic therapy is prescribed.

C. Management of CDH.

1. **CM.** If MOH is potentially a factor, the symptomatic medication overuse should be dealt with and an appropriate regimen for acute headache treatment initiated. If the CM is complicated by depression, an anxiety disorder or chronically disrupted sleep, appropriate treatment for the relevant comorbidity similarly should be initiated.

   Only two prophylactic therapies, to piramate and onabotA, currently can claim at least a reasonably solid scientific basis for their use in treating CM; both have been discussed previously in some detail. Reasonable alternatives that possess a decidedly thinner evidence base include gabapentin, VPA, tizanidine, amitriptyline, and occipital nerve blocks.

   Nonpharmacologic interventions may assist in suppressing CM. In particular, research has indicated a clear association between aerobic conditioning and remission of CM to episodic migraine. Although obesity appears to correlate strongly with migraine "chronification," it is as yet unknown whether weight reduction may represent an effective therapy for individuals with CM.

2. **Pure CTTH.** "Pure" CTTH typically lacks the severe intensity of migraine headache and the associated migrainous features of photophobia, phonophobia, nausea, vomiting, diarrhea, or aura. These patients typically have a continuous or near-continuous headache of mild-to-moderate intensity that is annoying and uncomfortable but does not limit activity. Some patients with pure CTTH may respond to preventative antimigraine agents but most do not; in one large-scale clinical trial, onabotA injection therapy was clearly ineffective for CTTH.

   Tizanidine in a dose of 8 to 24 mg per day may be beneficial for some patients; in one study a scheduled three times daily dosing schedule (mean dose 18 mg total daily) appeared to be effective in treating CDH (of various etiologies), but many patients find such treatment too sedating. TCAs and various NSAIDs commonly are prescribed as prophylactic therapy to patients with CTTH, but established evidence of benefit is sparse at best. Occipital nerve blocks or other neck-centered interventions (e.g., deep tissue massage) may offer relief to patients whose CTTH possesses a prominent cervicogenic component.

   Nonpharmacologic measures such as biofeedback, other forms of cognitive-behavioral therapy, and physical therapy may help. Occasional subjects may respond to a vigorous exercise program.

   Put simply, the pathophysiology of CTTH remains obscure, and the disorder is difficult to treat. Afflicted patients frequently are treatment-refractory and continue to experience CDH for years. Interestingly, this group typically continues to work, whereas for CM missing work and chronic disability are common.

VI. GUIDELINES FOR REFERRING PATIENTS WITH CHRONIC OR RECURRENT PAROXYSMAL HEADACHE

Many headache patients can be treated effectively by primary care providers (PCPs), but specialized care sometimes is needed. One commonly asked question is when a patient should be referred to a headache specialist. Situations that may warrant referral include the following:

A. New, unexplained headache.

B. New, unexplained change in headache pattern/characteristics or neurologic signs on exam.

C. Poor response to those treatments with which the referring physician is comfortable.

D. Any situation in which the referring physician is uncomfortable with the patient for medical or psychological reasons.

E. Presence of comorbid medical or psychiatric condition whose management lies beyond the physician's expertise.

If the patient has a headache that is sufficiently severe, persistent, or both and the PCP is unable to arrive at an acceptably plausible diagnosis, referral to, a specialist with greater knowledge of headache diagnosis may be indicated.

If the patient has new or progressive neurologic findings of unknown origin, he/she should be seen by a physician with particular expertise in evaluating neurologic disorders.

If the PCP is simply unable to provide the patient with adequate relief, referral should be considered.

Patients with chronic diseases often "doctor shop" to see whether another provider can supply more effective treatment. If the patient requests a referral, it is usually best to proceed (graciously) with the referral. The patient will respect the physician for assisting him/her in continuing the search for pain relief. The physician's ready willingness to refer for a second opinion demonstrates to the patient that the physician's first concern is the patient's well-being.

There are many specialized headache centers and clinics throughout the United States. The American Headache Society and the American Council of Headache Education can provide patients with information about these centers. The address for both organizations is 19 Mantua Rd, Mt. Royal, NJ 08061.

Recommended Readings

Cady RK, Lipton RB, Hall C, et al. Treatment of mild headache in disabled migraine sufferers: results of the SPECTRUM study. *Headache.* 2000;40:792–797.

Cohen AS. Matharu MS, Goadsby PJ. Trigeminal autonomic cephalalgias: current and future treatments. *Headache.* 2007;47:969–980.

Couch J. Cluster headache: characteristics and treatment. *Semin Neurol.* 1982;2:30–40.

Couch J. Complexities of presentation and pathogenesis of migraine headache. In: Cady RK, Fox AW, eds. *Treating the Headache Patient.* New York, NY: Marcel Dekker; 1995:15–40.

Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine:pooled analysis of the 56-week PREEMPT. *Headache.* 2010;50:921–936.

Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia.* 2002;22(8):633–658.

Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT (1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet.* 2001;358(9294):1668–1675.

Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. *N Engl J Med.* 2002;346(4):257–270.

Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia.* 2004;24(suppl 1):9–160.

Lenaerts ME, Couch JR. Medication overuse headache. *Minerva Medica.* 2007;98:221–231.

Schürks M, Diener HC, Goadsby PJ. Update on the prophylaxis of migraine. *Curr Therap Options in Neurol.* 2008;10:20–29.

Silberstein SD. The pharmacology of ergotamine and dihydroergotamine. *Headache.* 1997;37(suppl):S15–S25.

Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). *Neurology.* 2000;55:754–762.

CHAPTER

50 Chronic Pain

Maunak Rana and W. Scott Jellish

The International Association for the Study of Pain defines chronic pain as pain that is present for 3 months beyond the inciting event. Persistent pain is a serious health problem because it dramatically impacts the **economic, physical,** and **bio-psychosocial** well-being of society. This chapter presents an overview of the classification and treatment of chronic pain states.

I. TYPES OF CHRONIC PAIN

The sensation of pain can be broadly classified into "neuropathic, musculoskeletal, and psychological."

A. Neuropathic pain is described as "electric, burning, or shock-like." Sources of neuropathic pain can be metabolic, nutritional, infectious, genetic, autoimmune, and vasculitic in nature. These problems can lead to muscle cramps, numbness, and weakness of an affected extremity, causing mononeuropathy or polyneuropathy.

B. Musculoskeletal pain is described as "aching" (superficial or deep). Discomfort is associated with muscle spasms and a decreased range of motion. If persistent, pain may lead to disuse atrophy and contractures. Causes include myofascial pain, fibromyalgia, posttraumatic/iatrogenic, myopathy, metabolic bone/muscle disease, and/or intervertebral disc disease.

C. Psychological pain may present as any of the above. Patients may also describe difficulty sleeping, diminished physical, mental, and social functions. Treatment involves addressing the problem with the patient and acknowledging that depression and anxiety may be part of chronic pain, which requires treatment. Primary psychological derangement or a secondary underlying cause of chronic pain may be the problem.

II. MANAGEMENT OF CHRONIC PAIN

Treatment for chronic pain may involve pharmacologic therapy, interventional options, and biofeedback.

A. Medications.

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs).** These agents lead to analgesia via central and peripheral mechanisms. They function through the inhibition of the arachidonic acid cascade, which leads to decreased production of prostaglandins. Patients may have varying responses to different agents in this class. These agents can be classified based on their action against **cyclooxygenase I/II activity (COX).** COX I/II nonselective agents include ibuprofen, naproxen, and piroxicam. Celecoxib is currently the only COX II selective agent available in the United States. parecoxib, an intravenous COX II selective agent, is not currently available in the United States. Common side effects of NSAIDs include renal dysfunction, gastrointestinal (GI) bleeding, and ulcer formation. The antiplatelet effects are not seen with celecoxib and other COX II selective agents.
2. **Opioids.** These drugs are either naturally occurring alkaloids or are synthetically produced. They function, to varying degrees, at opioid receptors in the CNS and periphery. These agents are classified based on chemical structure. Opium plant derivatives (**phenanthrenes**) include morphine and codeine. Agents that are synthetically derived from the phenanthrenes (**semi-synthetic**) are hydrocodone, oxymorphone, and oxycodone. Synthetic agents not derived from the phenanthrenes include the **aniliodopiperidines,** fentanyl

(transdermal, buccal, and sublingual), sufentanil, and remifentanil. The **phenylpiperidines** are meperidine and tramadol**; phenylpropylamines** include propoxyphene, methadone, and loperamide. Pentazocine is a **benzomorphane, oripavine** (buprenorphine), and **morphinan** drugs include butorphanol and nalbuphine. Buprenorphine is an opioid receptor agonist/antagonist that has also been used in pain management (Table 50.1).

Clinicians should utilize preparations with the least abuse potential and side effects. Agents that contain an anti-inflammatory/acetaminophen, to decrease the dose of opioid required for analgesia, should be considered first-line drugs. Common side effects of opioids include respiratory depression, sedation, cognitive impairment, liver dysfunction, and testosterone deficiency in men both with long-term use. Tolerance, addiction potential, and withdrawal from sudden cessation are also common.

3. **Antidepressants.** Antidepressants are also utilized in chronic pain management. These agents act via mechanisms that include a direct antidepressant effect, a decrease in synaptic transmission, and the enhancement of the action of endogenous opioids (Table 50.2). They are classified based on their mechanism of action. Tricyclic antidepressants include amitriptyline and nortriptyline. Common side effects of these agents include dry mouth, sedation, sexual dysfunction, hyponatremia, and the risk of withdrawal if discontinued. Selective serotonin reuptake inhibitors (SSRI) are another class of antidepressant and include fluoxetine and duloxitene. Duloxetine is a dopamine, serotonin, and norepinephrine reuptake inhibitor. This drug is used for diabetic neuropathy and is contraindicated in patients with concomitant monoamine oxidase inhibitor therapy, hypersensitivity, and narrow angle glaucoma. Common side effects of SSRI agents include dry mouth, constipation, orthostatic hypotension, weight gain, dizziness, unmasking of mania in bipolar patients, and risk of seizures in patients receiving tramadol. Other agents in this class include buproprion, trazadone, and venlafaxine. Clinicians should be aware that lower doses of antidepressants are usually used for analgesia.
4. **Anticonvulsants.** Anticonvulsants are also used in the treatment of chronic painful conditions. Many agents in this category have a common historical use for the prevention and suppression of seizure disorders. These drugs act via different mechanisms including **increasing inhibitory neurotransmitters, decreasing excitatory transmitters,** and **blocking ion channels.** These agents are most effective for neuropathic pain, although medications of the other classes may be utilized (Table 50.2).

Phenytoin is used to treat diabetic neuropathy. Treatment is initiated at 300 mg per day, with increased dosage as needed. Side effects include gingival hyperplasia, hirsutism, acne, and coarsening of features. This agent activates the P-450 enzyme system in the liver, resulting in a decreased efficacy of mexiletine, haloperidol, and carbamazepine. Co-administration with antidepressants may lead to increased blood levels of phenytoin.

Carbamazepine is used for trigeminal neuralgia (tic douloureux), post-stroke pain, post-herpetic neuralgia, and diabetic neuropathy. The drug is believed to act via central and peripheral mechanisms, selectively targeting actively firing C and A delta fibers. Treatment is started at 100 mg twice a day and titrated to effect. The typical dose range is 300 to 1,000 mg per day in divided doses. Side effects include gait alterations, hyponatremia, leukopenia, aplastic anemia, and agranulocytosis. As a result of these potential hematologic alterations, blood tests are recommended every 2 to 4 months. Oxcarbazepine is an analogue of carbamazepine less likely to cause CNS/blood alterations. Side effects include hyponatremia (sodium of <125 mmol per L), sedation, and dizziness.

Lamotrigine prevents the release of glutamate in addition to blocking active sodium channels. This agent is used for cold-induced discomfort, trigeminal neuralgia, diabetic, and HIV neuropathy. The starting dose is 20 to 50 mg at bedtime, slowly increased to 300 to 500 mg per day in twice daily divided doses (over 2 weeks). A rash, the most common side effect, is commonly seen in pediatric patients, patients receiving valproic acid, and in patients receiving rapid titration of lamictal. The rash may also lead to Stevens–Johnson syndrome. Clinicians should note a decreased efficacy of lamotrigine with concomitant administration of carbamazepine and phenytoin.

Topiramate acts at both sodium and calcium channels, enhancing the action of gamma-aminobutyric acid (GABA), and inhibiting AMPA receptors. The agent is used in diabetic neuropathy, post-herpetic and intercostal neuralgia, and complex regional pain

TABLE 50.1 Narcotics

Drug	Starting Dose	Goal Dose	Side Effects
Morphine (available in immediate release, continuous extended release, and elixir)	15–30 mg q4h immediate release	Use preparation with least abuse potential	Respiratory distress
Codeine (available in various combinations with acetaminophen)	15–60 mg PO q4–6h, not to exceed 360 mg/24 hr	Use combination agents that contain an anti-inflammatory to decrease opioid dose	Sedative, cognitive impairment
Oxycodone (also available with acetaminophen—percocet)	10–30 mg q4h	May utilize narcotic contract to control abuse	Liver dysfunction with long-term use
Oxymorphone	1 mg IV q4–6h		Testosterone deficiency
Hydrocodone (available with acetaminophen—norco, vicodin, lorbab, available with ibuprofen–vicoprofen)	1 tablet q4–6h, not to exceed 3–4 g of acetaminophen q.d.		Tolerance
Fentanyl	Patch: start @ 25 mcg/q72h		Addiction potential
Meperidine	15–35 mg/hr IV		Withdrawal with cessation
Tramadol (also available in combination with acetaminophen)	50–100 mg PO q.i.d., max 400 q.d. if >75 y, hepatic or renal dysfunction, max daily dose 200 mg/q.d.		
Propoxyphene	65 mg q4h		
Methadone and loperamide	2.5–10 mg q8–12h		
Pentazocin in formulation with aspirin and/or naloxone	1 tablet q4h p.r.n.		
Buprenorphine (also available in formulation with naloxone)	Variable with formulation		
Butorphanol	1–4 mg q3–4h by MDI		
Nalbuphine	10 mg/70 kg body wt 3–4 hr p.r.n. Total daily dose ≤160 mg/q.d.		

Abbreviations: q.d., every day; p.r.n., as needed.

syndrome (CRPS) (see Chapter 51). Dosing is begun at 50 mg at bedtime, increasing to 200 mg twice daily. Side effects include sedation, development of kidney stones, and ocular granuloma due to the inhibition of carbonic anhydrase.

A final channel blocking agent, levetiracetam is started at 500 mg PO twice daily and adjusted to a target of 1,500 mg twice a day. Side effects include rash, hives, itching, and dizziness.

5. **Local anesthetics.** Lidocaine is available in salve and patch (5%) forms. It is used for post-herpetic neuralgia, post-thoracotomy pain, intercostal neuralgia, and fibromyalgia. The drug is started at 1 to 5 mg per kg intravenously. The patch is used 12 hours per day and may be cut to size and shape. Side effects of lidocaine include bradycardia, dizziness (at plasma level of 10 mg per ml), cardiac depression (at 20 to 25 mg per ml plasma level), blurred vision, and seizures. Mexiletine, an oral analogue of lidocaine, is used for post-stroke pain, myotonia, spasticity, and diabetic neuropathy. Treatment is initiated at 150 mg per day up to a goal of 300 to 450 mg per day. The side effect profile is similar to lidocaine.
6. **Calcium channel blockers.** Gabapentin is a membrane stabilizer which binds at the alpha-2 delta subunit of the L-calcium channel (Table 50.2). Gabapentin is used for many neuropathic pain states including diabetic neuropathy, post-herpetic neuralgia, and complex regional pain syndrome (CRPS). Treatment is started at 100 to 300 mg at bedtime, increasing to 4,800 mg per day divided in three doses. Common side effects include fatigue, somnolence, and dizziness.

   Pregabalin also binds to the alpha-2-delta subunit at voltage-dependent calcium channels. This agent is used for neuropathic pain states and for fibromyalgia. The starting dose of pregabalin is 150 mg per day titrated to 600 mg per day for neuropathic pain states; for fibromyalgia, the maximum daily dose is 450 mg per day. Side effects include dizziness, blurred vision, weight gain, and diminished cognition.

   Zonisamide acts at T-calcium and sodium channels. This drug increases GABA release. Zonisamide is started at 100 mg daily and increased after 2 weeks by 200 mg per week for a goal of 600 mg per day. Common side effects include ataxia, rash, kidney stones (carbonic anhydrase inhibitor), oligohydramnios, and pediatric hyperthermia.

   v-Conopeptides (ziconotide) acts on N-type calcium channels. Used intrathecally at 0.3 to 1 ng/kg/hour. The drug has been studied in cancer and HIV populations. Side effects include sedation, tremor, hypotension, and histaminergic reaction. Nimodipine, diltiazem, verapamil, and nifedipine are agents typically used for blood pressure control but may also have a role with other agents in pain management.
7. **Gabaergic agents.** Baclofen is a derivative of GABA with activity at GABA-b channels. It has both spinal and supraspinal activity (Table 50.2). This drug is used for spinal cord injury and spasticity. Initial therapy begins at 5 mg three times a day with titration to a daily dose of 80 to 100 mg. Baclofen may also be given intrathecally. Common side effects include confusion, ataxia, and hallucinations. Sudden cessation of therapy may lead to a withdrawal, which may be life-threatening.

   Tiagabine acts as a GABA reuptake inhibitor. The drug is started at 4 mg daily and increased by 4 to 8 mg per day to a final goal of 12 to 22 mg per day for patients not on antiepileptic drugs (AED), or 32 to 52 mg per day for patients on AEDs. Common side effects include risk of seizures in patients without a history of seizure disorder, aphasia, and sedation.

   Diazepam is a benzodiazepine and muscle relaxant that enhances the inhibitory action of GABA-A receptors especially in patients with spinal cord disease and muscle spasms. Diazepam is usually started at 2 mg twice daily to a total dose of 20 to 30 mg per day. Side effects include sedation and dependence. A withdrawal or sudden cessation may lead to seizures and death.
8. **Muscle relaxants.** Tizanidine is a centrally active alpha-2 adrenergic agonist used for spasticity, spinal cord injury, and post-stroke pain (Table 50.2). Dosing starts at 4 mg per day and is increased by 4 to 6 mg per week to a total of 36 mg per day. Side effects include headache, digestive changes, and dry mouth. Clinicians should exercise caution with concomitant use of other alpha-2 agonists because of the risk of hypotension. Cyclobenzaprine is a muscle relaxant that primarily acts at the brainstem, although it is not effective for centrally mediated spastic states. The dose is 30 to 40 mg per day and side effects include sedation and dry mouth.

TABLE 50.2 **Non-Narcotics**

Drug	Use	Starting Dose	Goal Dose	Side Effects
Amitriptyline	Neuropathic pain	50 mg q.h.s.	150 mg q.h.s.	Sedation, dry mouth, impotence, hyponatremia, withdrawal
Nortriptyline		25 mg pq q.h.s.	150 mg q.h.s.	
Duloxetine	Diabetic neuropathic pain	60 mg q.d.	120 mg q.d.	Dry mouth constipation, orthostatic hypotension, weight gain, dizziness, unmasking of mania in bipolar patients, and seizure risk in patients on tramadol
Phenytoin	Diabetic neuropathy	300 mg/d	300–400 mg/d	Gingival hyperplasia, hirsutism, coarsening of features
Carbamazepine	Trigeminal neuralgia, post-stroke pain, post-herpetic neuralgia, neuropathy	100 mg b.i.d.	300–1,000 mg/d in divided doses	Gait disturbances, hyponatremia, leucopenia, aplastic anemia, agranulocytosis
Lamotrigine	Cold-induced pain, trigeminal neuralgia, neuropathy	20–50 mg PO q.h.s.	300–500 mg/d in divided b.i.d. doses over 2 wk	Rash, Stevens–Johnson syndrome, decreased efficacy with coadministration of carbamazepine, phenytoin
Topiramate	Diabetic neuropathy, post-herpetic neuralgia, intercostal neuralgia, CRPS	50 mg q.h.s.	200 mg PO b.i.d.	Sedation, kidney stone, ocular granuloma
Levetiracetam	Neuropathic pain	500 mg PO b.i.d.	1,500 mg b.i.d.	Rash, hives, itching, dizzinesss
Gabapentin	Diabetic neuropathy, post-herpetic neuralgia, CRPS	100–300 mg q.h.s.	4,800 mg PO divided in t.i.d. dosing	Fatigue, somnolence, dizziness
Pregabalin	Neuropathic pains, fibromyalgia	150 mg/d	600 mg/d for neuropathic pain; 450 mg/d for fibromyalgia	Dizziness, blurred vision, weight gain, diminished cognition

Drug	Use	Starting Dose	Goal Dose	Side Effects
Zonisamide	Neuropathic pain	100 mg/d	600 mg/d	Ataxia, rash, kidney stones, oligohydramnios, pediatric hyperthermia
ω-conopeptide	Cancer pain, HIV neuropathy	0-3-1 ng/hr		Sedation, tremor, hypotension, histaminergic reaction
Baclofen	Spinal cord injury, spasticity	5 mg t.i.d.	80–100 mg/d in divided doses	Confusion, ataxia, hallucinations, life-threatening withdrawal
Tiagabine	Neuropathic pain, spasticity	4 mg q.d.	12–22 mg/q.d. for pts not on epileptic drugs	
			32–53 mg/q.d. for pts one AEDs	Seizures, aphasia, sedation
Diazepam	Muscle spasms, spasticity	2 mg b.i.d.	20–30 mg/q.d.	Sedation, dependence, risk of seizure and death with withdrawal
Tizanidine	Muscle spasms, spasticity, spinal cord injury, post-stroke pain	4 mg/q.d.	Increase by 4–6 mg/wk to 36 mg/q.d.	Headache, digestive changes, dry mouth
Cyclobenzaprine	Muscle spasms	30–40 mg/q.d.	30–40 mg/q.d.	Sedation, dry mouth
Chlorzoxasone	Muscle spasms	250 mg t.i.d./q.i.d.	1,000–2,000 mg/qd	GI disturbances, liver dysfunction, sedation
Carisoprodol	Muscle spasms, spasticity	350 mg t.i.d./q.i.d.	350 mg po t.i.d./q.i.d.	Sedation, tremor, altered cognition, addiction potential
Methocarbamol	Muscle spasms	1,000 mg/t.i.d.	3,000–4,000 mg/q.d.	Sedation, altered cognition
Metaxolone	Muscle spasms	800 mg t.i.d./q.i.d.	800 mg t.i.d./q.i.d.	Hemolytic anemia, elevated liver function tests
Orphenadrine	Neuropathic pain, muscle spasms	60–80 mg q8h	60–80 mg q8h	Orthostatic hypotension, urinary retention, dizziness, euphoria
Botulinum toxin	Dystonia, spasticity, migraine, torticollis, myofascial pain, GI, GU spasms	Varies based on site of injection		Myalgias, dysphagia, discomfort

Abbreviations: b.i.d., twice a day; t.i.d., three times a day; q.i.d., four times a day.

Chlorzoxazone is centrally acting with a target dose of 1,000 to 2,000 mg per day. Side effects include GI disturbances, sedation, and liver dysfunction. Carisoprodol is a muscle relaxant that acts centrally at the reticular activating system and the spinal cord. The treatment goal is 350 mg three to four times a day. Side effects include sedation, tremor, altered cognition, and possible addiction potential. Methocarbamol is used at 3,000 to 4,000 mg per day. Metaxolone is dosed at 800 mg three to four times a day. This drug may lead to hemolytic anemia and elevated liver function tests.

Orphenadrine is an NMDA receptor antagonist with anticholinergic effects. It acts via central and peripheral mechanisms. This drug is used for neuropathic pain and muscle spasms. It potentiates the analgesic effects of opioids. Orphenadrine is started at 60 to 80 mg every 8 hours. Side effects include orthostatic hypotension, urinary retention, dizziness, and euphoria.

Botulinum toxin is a muscle relaxant that acts at the neuromuscular junction and inhibits the release of acetylcholine presynaptically. Its effect lasts for approximately 3 months. This agent is used for dystonia (writer's cramp and musician's cramp), spasticity, migraine headaches, hyperhidrosis, myofascial pain, GI and genitourinary (GU) spasm. It should not be used in patients with neuromuscular junction/motor neuron dysfunction such as in myasthenia gravis, Lambert–Eaton myasthenic syndrome, and amyotrophic lateral sclerosis. Side effects include myalgia, dysphagia, and local discomfort. The amount of agent injected is tailored to the site of injection, degree of spasm and the musculature being injected.

9. **Other agents.** Clonidine is an alpha-2 agonist that potentiates the analgesic action of opioids. It is useful for neuropathic pain. A transdermal patch is started at a dose of 0.1 mg per day and changed every 7 days. Side effects include sedation, dry mouth, and orthostatic hypotension. Capsaicin, an extract of chili pepper, is thought to cause analgesia by depletion of substance P. Clinicians should note that application may lead to discomfort and irritation prior to analgesia.

B. Nonpharmacologic treatments.

1. **Physical therapy and occupational therapy.** The use of heat, ultrasound, electrical stimulation, and deep tissue massage may reduce the discomfort associated with chronic pain states. The mainstay of treatment for certain conditions, including CRPS, is range of motion and physical therapy. Prevention of contracture is important in maintaining function and decreasing discomfort.
2. **Electrical stimulation** involves the use of either **transcutaneous electrical nerve stimulation, spinal cord (dorsal column),** or **thalamic stimulators,** which can modulate pain. Patients with neuropathic pain states, muscular pain, central pain, and axial low back pain may benefit from these therapies. The classical "gate control" theory postulates that stimulation of large fiber (a beta) neurons closes the gate that has been opened or initiated by the smaller diameter nociceptors. Contraindications for these therapies include pregnancy and the presence of a pacemaker.
3. **Psychological treatment** is an important component of the patient's overall chronic pain treatment plan. A support network for the patient, involving family and friends, may be conducive to the healing process. Additionally, the use of biofeedback along with adjunctive physical therapy may help a patient with their discomfort.

Finally, the ultimate goal in the management of a patient with chronic pain is the precise diagnosis with appropriate treatment for the painful condition. Referral to an interventional pain physician may benefit the patient after conservative therapy has failed. Disease processes difficult to treat, such as CPRS, diabetic neuropathy, and peripheral neuropathies, may be addressed with a specialist versed in providing interventional modalities along with pharmacotherapy. Physical therapy is also vital to the patient's treatment in decreasing discomfort. As the primary care provider, it is crucial to have honest communication with the patient about treatment goals, expectations, and the possibility of achieving those expectations.

Recommended Readings

Benzon H, Raja S, Molloy R, et al., eds. *Essentials of Pain Medicine and Regional Anesthesia*. 2nd ed. Philadelphia, PA: Elsevier; 2005.

Dickenson AH, Ghandehari J. Anticonvulsants and antidepressants. *Handb Exp Pharmacol*. 2007;177:145–177.

Ettinger AB, Argoff CE. Use of antiepileptic drugs for nonepileptic conditions: psychiatric disorders and chronic pain. *Neurother*. 2007;4:75–83.

Loeser JD, Chapman CR, Fordyce WE, eds. *The Management of Pain*. 2nd ed. Philadelphia, PA: Lea & Feibiger; 1990.

McMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5th ed. Philadelphia, PA: Elsevier/Churchill Livingstone; 2005.

Nikolaus T, Zeyfang A. Pharmacological treatments for persistent non-malignant pain in older persons. *Drugs Aging*. 2004;21:19–41.

Sullivan MD, Robinson JP. Antidepressant and anticonvulsant medications in chronic pain. *Phys Med Rehabil Clin N Am*. 2006;17:381–400.

Wallace JM. Update on the pharmacotherapy guidelines for treatment of neuropathic pain. *Curr Pain Headache Rep*. 2007;11:208–214.

CHAPTER

51 Complex Regional Pain Syndrome

Jasvinder Chawla and Venkata Reddy

The International Association for the Study of Pain (IASP) suggests the terms **complex regional pain syndrome** type I (CRPS type I) for reflex sympathetic dystrophy and CRPS type II for causalgia. The sole differentiating criterion between CRPS type I and type II is the presence of a known nerve injury in CRPS type II. CRPS type I usually follows an initiating noxious event, is not limited to the distribution of a single nerve, and is apparently disproportionate to the inciting event. At some point, there is associated edema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, allodynia, or hyperalgesia. CRPS type I is associated with a variety of precipitating factors (Table 51.1); trauma is the most common precipitating event (Fig. 51.1A and B).

I. PATHOPHYSIOLOGY

Various hypotheses include peripheral mechanisms, central mechanisms, or psychogenic factors.

A. Peripheral mechanisms do not address the spread of pain beyond a dermatomal territory and pain occurring in patients without nerve injury. They are of four types.

1. After an inciting event, a subset of **C-polymodal nociceptors** develop sensitivity to sympathetic stimulation and thus may be stimulated by noradrenalin. An alternative explanation is that noradrenalin may act indirectly through the release of prostaglandins that stimulate the nociceptors.
2. Sympathetic efferents cause abnormal activation of peripheral nociceptors.
3. Aberrant nerve sprouts generated at the site of injury develop into neuromas.
4. Artificial synapses form at the site of nerve injury and allow "ephaptic" transmission between sympathetic efferent and sensory afferent fibers.

B. Central mechanisms are of two types.

1. Self-sustaining loops of abnormal interneuronal firing in the dorsal horn, after being propagated by a peripheral irritative focus, give rise to ascending projections of pain and descending sympathetic hyperactivity.
2. Long-term sensitization or "wind-up" of wide-dynamic-range neurons in the spinal cord resulting from ongoing nociceptive stimulation from the periphery. The sensitized wide-dynamic-range neurons then respond to activity in large diameter A-mechanoreceptors that are activated by light touch. The pain threshold is reduced and previously subthreshold stimuli are then perceived as painful.

C. Psychogenic factors. A major issue in the diagnosis and management of CRPS is the lack of properly controlled comparison studies of placebo with sympathetic blockade. Furthermore, a fair number of patients with neuropathic pain improve with injections of placebo. In some patients, symptoms may be conversion–somatization of an underlying psychiatric condition, because these patients seem to respond to cognitive psychotherapy.

II. DIAGNOSIS AND COURSE

A. Diagnosis.

1. **IASP diagnostic criteria include the following:**
   a. Presence of an initiating noxious event or a cause of immobilization.
   b. Persistent pain, allodynia, or hyperalgesia, with ongoing pain disproportionate to the inciting event.

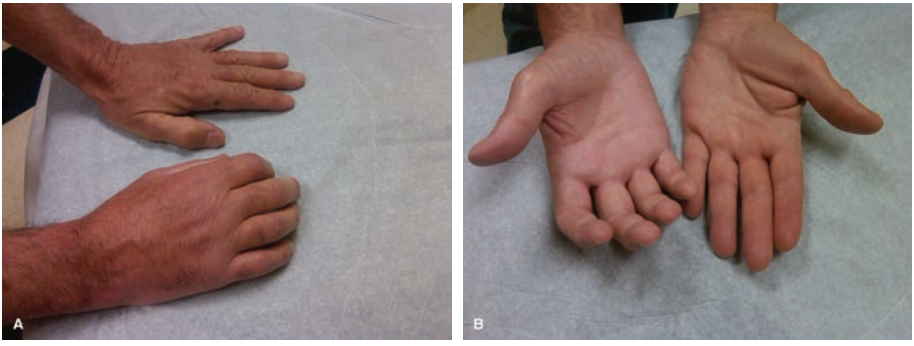

FIGURE 51.1 **A:** and **B:** A 59-year old man was drilling a hole in concrete when the drill kicked back and jerked his hand. Patient did not seek medical care for 2 weeks. When he did seek medical care, he found he had crushed two wrist bones, the trapezium, and triquetral. The patient was casted for 4 weeks and then developed severe pain and soreness of the right hand. On examination the dorsum of the right hand was purplish-reddish and very shiny, and there was more hair on the right hand than on the left. (Courtesy of Dr. Jose Biller.)

TABLE 51.1 Precipitating Factors in the Development of CRPS Type I

Soft-Tissue Injury	Malignancy
Fracture	Arthritis
Sprain	Bursitis
Joint dislocation	Peripheral nerve injury
Operative procedures	Carpal tunnel release
Immobilization with a cast or splint	Venipuncture
Arthroscopic surgery	Myocardial infarction
Brachial plexopathy	Polymyalgia rheumatica
Radiculopathy	Myelopathy
Stroke	Dental extraction
Spinal cord injury	Prolonged bed rest
Drugs (isoniazid, phenobarbital, ergotamine and cyclosporine)	

c. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.
d. Diagnosis excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Criteria (b) through (d) must be satisfied.

2. **Modified diagnostic criteria.** A study validated the IASP diagnostic criteria but showed that the CRPS criteria have inadequate specificity and are likely to lead to overdiagnosis. The investigators proposed the following **modified research diagnostic criteria** for CRPS:
   a. Continuing pain disproportionate to any inciting event.
   b. At least one symptom in each of the four following categories:
      (1) **Sensory:** hyperesthesia.
      (2) **Vasomotor:** temperature asymmetry, skin color changes, skin color asymmetry, or a combination of these signs.
      (3) **Sudomotor edema:** edema, sweating changes, sweating asymmetry, or combination of these symptoms.
      (4) **Motor/trophic:** decreased range of motion, motor dysfunction (weakness, tremor, and dystonia), trophic changes (hair, nails, and skin), or a combination of these symptoms.

c. At least one sign in two or more of the following categories:
   (1) **Sensory:** evidence of hyperalgesia to pin prick or allodynia to light touch.
   (2) **Vasomotor:** evidence of temperature asymmetry, skin color changes, asymmetry, or a combination of these signs.
   (3) **Sudomotor/edema:** evidence of edema, sweating changes, sweating asymmetry, or a combination of these symptoms.
   (4) **Motor/trophic:** evidence of decreased range of motion, motor dysfunction (weakness, tremor, and dystonia), trophic changes (hair, nails, and skin), or a combination of these symptoms.

These research criteria may help prevent overdiagnosis of CRPS and may improve the ability to differentiate CRPS from other types of neuropathic pain.

3. Diagnosis of CRPS type I is generally made on the basis of **history and clinical findings. Laboratory testing is utilized to exclude other diagnosis.** Clinical features are summarized in Table 51.2. CRPS in children is often under recognized by physicians resulting in diagnostic delays. The lower extremities are more commonly affected than the upper extremities. Minor trauma remains the most frequent cause. The female preponderance is much greater among children than among adults; patients are typically pubertal adolescent girls.

   A therapeutic response to **sympathetic neural blockade** should be carefully evaluated to identify responders to this diagnostic procedure. The pain-relieving effect should outlast the expected 6- to 12-hour effect of the local anesthetic.
4. **Differential diagnosis.** CRPS type II (causalgia), unrecognized local lesions (e.g., fracture, strain, and sprain), traumatic vasospasm, cellulitis, Raynaud's disease, thromboangiitis obliterans, arterial/venous thrombosis, diabetic painful neuropathy, radicular syndromes, and gout.
5. **Methods** used to aid in difficult-to-diagnose cases of and various severities of CRPS type I include radiography and scintigraphy. Most laboratory tests for CRPS are based on detection of asymmetric vascular or sudomotor function between the affected and contralateral unaffected side.
   a. **Radiography.** Plain radiographs may show patchy osteopenia in one half of all patients. Plain radiography remains useful in detecting or excluding other bony abnormalities.
   b. **Scintigraphy.** A three-phase technetium bone scan (TPBS) is helpful in confirming the diagnosis and staging of CRPS type I. The sensitivity and specificity ranges from 54% to 100% and 85% to 98%, respectively. Given a variety of presentations of CRPS, a TPBS not only confirms the diagnosis, but it also helps exclude other diagnoses such as degenerative arthritis, benign or malignant bony lesions, or even metabolic bone diseases such as Paget's disease, osteomyelitis, stress fracture, bone infarction, Reiter's disease, and thoracic outlet syndrome, particularly if utilized in combination with SPECT/CT. A TPBS is used in three ways.
      (1) **Blood flow phase.** Rapid-sequence images of the involved extremity are obtained after intravenous (IV) injection of a radionuclide tracer to evaluate the vascularity of a region.

TABLE 51.2 Clinical Features of CRPS Type I

Feature	Example
Autonomic deregulation	Temperature, vasomotor, and sudomotor instability
Blood flow alterations	Hyperhydrosis, hypohydrosis, edema, and discoloration
Sensory abnormalities	Hyperalgesia burning pain, hyperpathia, allodynia, dysesthesia and hemisensory impairment
Motor dysfunction	Weakness, tremor, and dystonia
Trophic changes	Skin thinning, hair loss, brittle nails, and changes in structure of both superficial and deep tissues
Psychological disturbances	Anxiety, depression, and suicidal ideation
Radiologic changes	Patchy osteoporosis, soft-tissue edema, and articular erosion

(2) **Blood pool phase.** Images are obtained immediately after the blood flow phase to evaluate regional perfusion, including that of soft tissue.

(3) **Bone scan phase.** Static images are obtained 2 to 3 hours after initial injection to detect abnormal osteoblastic activity, reflected locally as increased periarticular uptake in the affected extremity.

c. **Quantitative sudomotor axon reflex testing (QSART).** Resting sweat output and stimulated sweat output as measured by QSART can help detect sudomotor asymmetry between the affected and contralateral unaffected side. Thermography and infrared thermometry are also used to measure skin temperature as an index of blood flow.

B. Course. CRPS type I can progress through three stages (Fig. 51.2).

1. **Stage 1 (acute).** Pain is described as aching or burning, aggravated by physical contact or emotional upset, and typically restricted to a vascular or peripheral nerve or root territory. Some patients report paresthesias or burning distal pain. Hyperalgesia may be present, as may allodynia to light touch, thermal stimulation, deep pressure, or joint movement. Tissue swelling and local vascular, bony, and trophic changes occur in the affected part. Radiography may show diffuse bony changes. TPBS may show increased radionuclide uptake in all phases. Stage 1 usually occurs 1 to 3 months after injury.
2. **Stage 2 (dystrophic)** is characterized by spontaneous burning pain radiating proximally or distally from the site of injury and associated with pronounced hyperpathia,

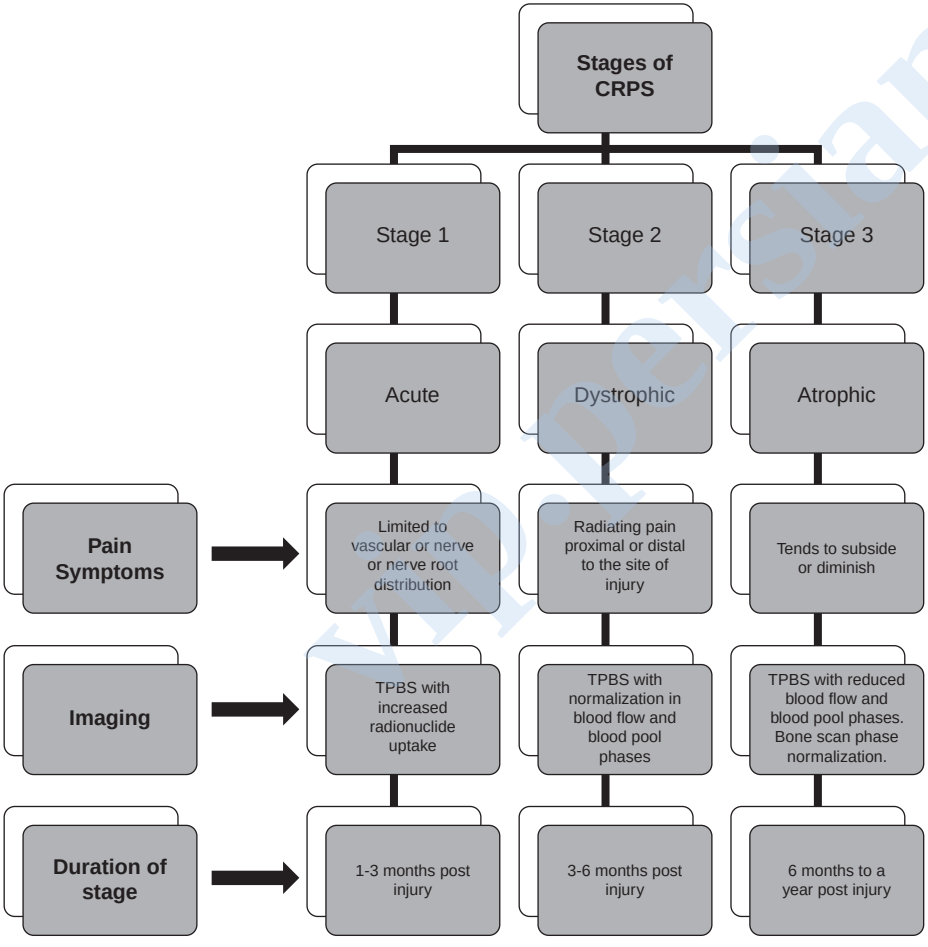

FIGURE 51.2 Stages and course of CRPS.

decreased hair growth, brittle nails, and indurated edematous tissue. Radiography may show patchy osteoporosis. TPBS shows normalization in the blood flow and blood pool phases. The bone scan phase remains intense. Stage 2 usually occurs 3 to 6 months after injury.

3. **Stage 3 (atrophic).** Pain tends to subside or diminish in intensity. The skin is cool, thin, and shiny. Irreversible trophic changes occur with subcutaneous atrophy and wasted fingertips. Radiographs may show severe patchy osteopenia. TPBS shows reduced blood flow and blood pool phases and bone scan phase normalization. Stage 3 usually occurs 6 months to years after injury.

III. PREVENTION

Prevention is best accomplished through early recognition and treatment. Unnecessary use of braces, casts, splints, and immobilization is best avoided. If CRPS type I is suspected, heat rather than cold should be applied. Alcohol is better avoided.

IV. MANAGEMENT

Treatment goals early in the course of the disease are cessation of aberrant sympathetic hyperactivity or hypoactivity, desensitization of normal sensory pathways transmitting pain, and maintenance of normal musculoskeletal function. Overviews of the various treatment modalities available for patients with CRPS are presented in Figure 51.3. Step-wise approach for the management of upper- and lower-extremity CRPS type I are presented in algorithms in Figures 51.4 and 51.5. Management is individualized, but overall could be divided into noninvasive and invasive methods.

Noninvasive Methods

A. Pharmacologic therapy.

1. **Abortive therapy.**
   a. **Anti-inflammatory agents.** Administration of nonsteroidal anti-inflammatory drugs (NSAIDs) usually is begun in the care of patients with early, mild symptoms, particularly when an inflammatory process (e.g., arthritis) is a component of the painful condition. Dosage should be maximized for optimal control of pain. NSAIDs are of minimal beneficial value, however, in the management of long-standing CRPS type I.
   b. **Systemic corticosteroids.** In addition to having anti-inflammatory effects, corticosteroids may have inhibitory effects on spontaneous neural discharge. The effects are only temporary, and these agents do not inhibit the sympathetic reflex mechanism in CRPS type I.
      (1) A standardized regimen of high initial dosage and subsequent tapering of dosage consists of **prednisone** (or an equivalent) at 15 mg four times a day, 10 mg four times a day, 10 mg three times a day, 10 mg twice a day, 15 mg every morning, 10 mg every morning, and 5 mg every morning for 4 days each.
      (2) Injections of depot steroids directly into inflamed muscles and joints may greatly reduce pain in an affected extremity and serve adjunctively as a therapy for CRPS type I.
      (3) Potential **harmful effects** of steroids include osteoporosis, hyperglycemia, adrenal suppression, glucose intolerance, and sodium and water retention.
   c. **Narcotic analgesics** rarely are needed in the management of CRPS type I. Intermittent use of narcotic analgesics as a prophylactic measure may be beneficial before exercise therapy. In severe, dystrophic stages associated with long-standing pain not controlled with other medical therapy or nerve block procedures, narcotic analgesics may become a necessary adjunct to long-term care. In such cases, administration by means of an intrathecal morphine pump may be appropriate. The risks of tolerance and dependence that attend long-term narcotic use must be carefully weighed against the benefits.

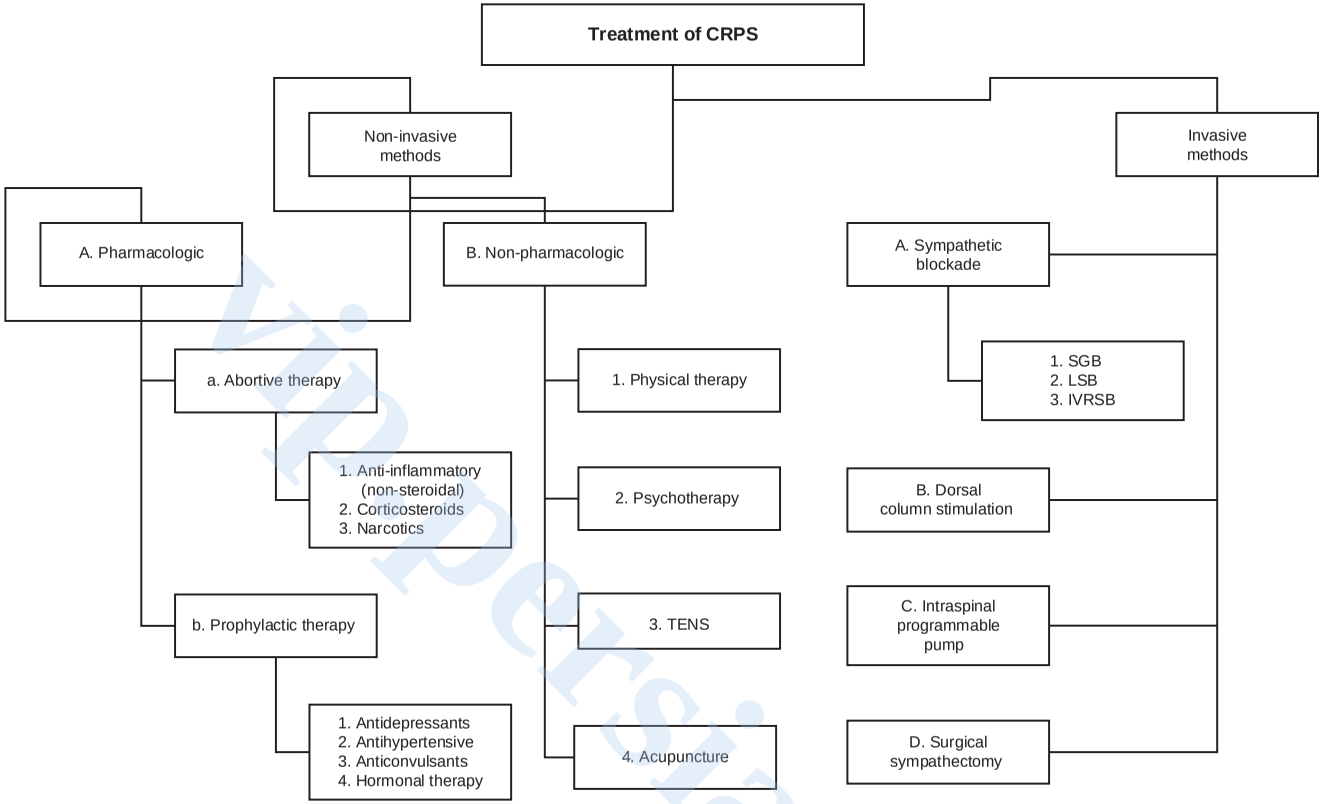

FIGURE 51.3 Overview of treatment options in patients with CRPS. *SGB*, stellate ganglion block; *LSB*, lumbar sympathetic block.

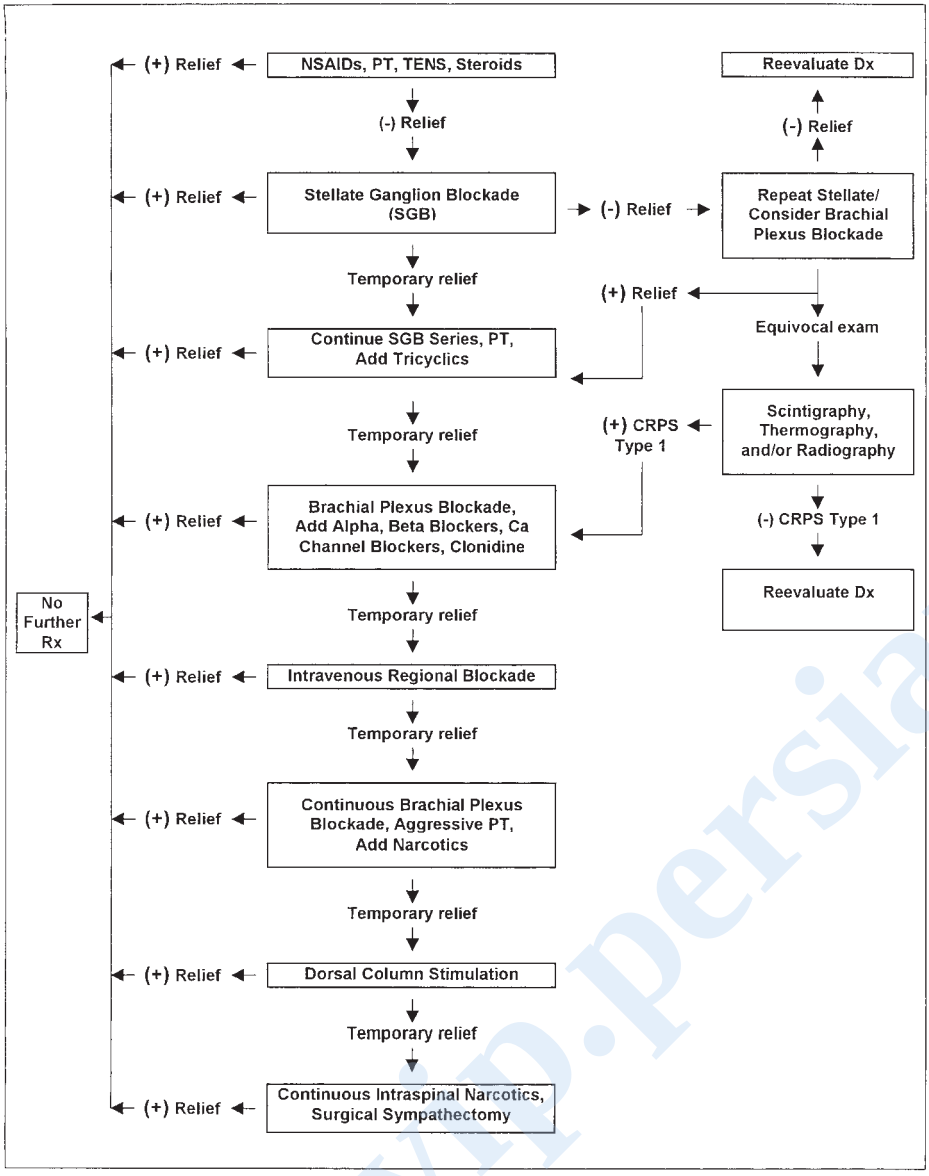

FIGURE 51.4 Upper-extremity CRPS algorithm. (+), present; (–), absent; *Dx*, diagnosis; *Rx*, treatment; *Ca*, calcium.

2. **Prophylactic therapy.**
   a. **Antidepressants** are effective adjuvants and are commonly used in CRPS type I. The choice of drug depends on the patient's medical profile and previous response to antidepressants.
      (1) **Amitriptyline** is the prototype tricyclic antidepressant and is the most widely used. Two weeks of treatment may be needed before the analgesic effect is observed. Treatment should begin with small doses of 10 to 25 mg at bedtime. The dose should be increased 10 to 25 mg every 1 to 2 weeks while the patient is examined for side effects until a beneficial effect is achieved or a maximum of 150 mg is reached.

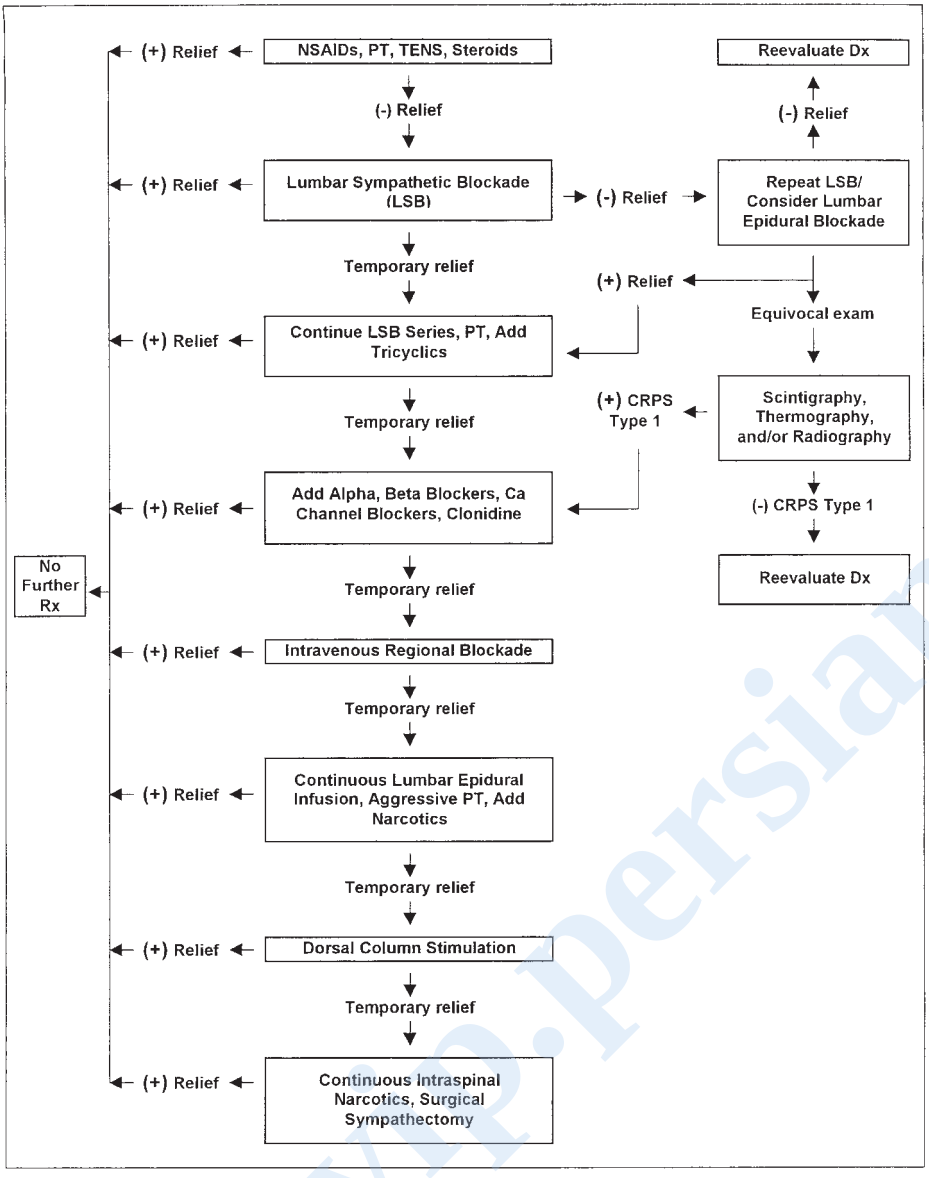

FIGURE 51.5 Lower-extremity CRPS algorithm.

(a) Antidepressants can interfere with the reuptake mechanism of bretylium, an agent commonly used in an IV regional sympathetic blockade (IVRSB) technique. Antidepressant therapy should be discontinued for at least 2 weeks before initiation of an IV bretylium block.

(b) **Complications** of antidepressant use includes sedation, orthostatic hypotension, dry mouth, blurred vision, and urinary retention.

b. **Antihypertensives.**

(1) **Calcium channel blockers** are used to manage in CRPS type I for their peripheral vasodilatory effects as well as their antagonistic effects with norepinephrine on arterial and venous smooth muscles.

(a) **Nifedipine** has the most vasodilatory effect of all the calcium channel blockers. A hypothermic extremity, as typically observed in CRPS type I, is an appropriate indication.
(b) **Side effects** of calcium channel blockers include an increase in pain, hypotension, myocardial depression, and cold intolerance as a result of peripheral vasodilatation.

(2) α_2-Agonists have been studied in recent years to determine their analgesic effects on chronic pain states.
(a) **Clonidine,** a centrally acting α_2-agonist, decreases sympathetic outflow and vasodilatation. Clonidine administered transdermally by means of application of a patch inhibits norepinephrine release from peripheral presynaptic adrenergic terminals. Clinically, it produces substantial reduction in hyperalgesia in response to mechanical stimuli confined primarily to the skin beneath the patch. Reports of systemic analgesic effects of clonidine are conflicting. Therefore, this agent may be most useful for patients with CRPS type I limited to only small areas. The recommended method of application is to place a patch over an area of allodynia, starting with 0.1 mg placed every 3 days and increasing the dosage in 0.1-mg increments every 12 days, to a dose of 0.3 mg. The skin should be checked for desensitization underneath the patch on replacement, and tolerance of side effects should be documented before the dosage is increased. The localized analgesia effect typically occurs within 36 to 48 hours and subsides within 1 week of discontinuance.
(b) Clonidine administered in a 300-mg dose within the epidural space produces effective analgesia for patients with refractory CRPS type I, but long-term relief has not been fully addressed.
(c) Significant **side effects** of clonidine include hypotension, bradycardia, and sedation.

(3) α_1-Antagonists have been shown to be of some help to patients with CRPS type I.
(a) **Terazosin,** an oral α_1-antagonist, appears to be effective for some patients and can be used in a once daily dosing regimen.
(b) Terazosin can be started at 1 mg at bedtime and titrated slowly upward to 3 mg at bedtime.
(c) Use of α-blockers is limited by their prominent side effects of hypotension, reflex tachycardia, fatigue, and dizziness.

c. **Anticonvulsants** stabilize abnormal hyperexcitability in both peripheral and central neurons and are thus hypothesized to inhibit excessive discharge of regional sympathetic nerves. Phenytoin at a dosage of 100 mg four times a day or carbamazepine at 200 mg three times a day may be used for the management of dysesthesia.
d. **Hormonal therapy—calcitonin,** given parenterally or intranasally, is widely used for CRPS type I pain in the United Kingdom. It has analgesic activity and inhibits bone resorption activity and therefore seems like a valuable aid in the management of certain types of osteoporosis.

B. Nonpharmacologic therapy.

1. **Physical therapy (PT)** is a useful adjunct in the management of CRPS type I. It is used to control and minimize dystrophic changes in muscles and joints. Compliance increases if adequate pain relief can be achieved before the initiation of PT.
   a. **Range-of-motion and stretching exercises** are used for the progressive stretching of restrictive tissue for maintenance of flexibility. Aggressive treatment in the early stages has been shown to improve prognosis. It is recommended to utilize sensory stimulation, particularly with self-massage in order to keep the involved part as mobile as possible from onset of the disease process.
   b. **Strengthening exercises** entail progressive resistance to the musculoskeletal system to maintain strength and coordination of the muscles. These exercises include isotonic, isometric, isokinetic, and aerobic exercises. If a lower extremity is involved, therapy should focus on a gradual increase in the weight-bearing capability of the limb.

c. **Deep friction massage** is useful as a desensitization technique in the care of patients who can tolerate such manipulation.
d. **PT** has been reported by many to be the mainstay of treatment for children.

2. **Psychotherapy.** Patients with CRPS type I experience a range of behavioral changes, including depression, anxiety, suicidal ideation, and drug addiction. Patients in whom these traits develop at or before the time of injury are considered at higher risk of development and maintenance of symptoms of CRPS type I. Therefore all such patients should be considered for psychological consultation. **Psychotherapeutic** management of CRPS type I includes counseling and cognitive-behavioral techniques.
   a. **Counseling** is a means whereby the patient is helped to cope with the pain, irrespective of how well it may be controlled with pharmacologic or physical treatments. The services of a psychiatrist, psychologist, or social worker are used when appropriate.
   b. **Cognitive-behavioral techniques** include biofeedback, relaxation, and hypnosis.
3. **Transcutaneous electrical nerve stimulation (TENS).** According to the gate theory put forth by Melzack and Wall in 1965, painful transmission from the periphery carried by afferent C fibers causes a loss of interneuronal large-diameter A-fiber inhibition in the dorsal horns of the spinal cord. Both sets of fibers synapse on interneurons in the substantia gelatinosa of laminae II and III before secondary fibers transmit across the midline to ascending tracts and eventually synapse in the thalamus and higher cortical centers. TENS is thought to provide pain relief by closing this gating mechanism through preferential stimulation of large-diameter A fibers and inhibition of the smaller fibers within the substantia gelatinosa or by causing the release of endorphins, enkephalins, or both. Overall, TENS relieves symptoms of CRPS type I for most children, but only for approximately 25% of adults.
4. **Alternative pain management.** Acupuncture has been proposed as a possible management strategy.

Invasive Methods

A. **Sympathetic blockade.** The mechanism of continued pain relief from sympathetic blockade is not completely understood. Relief of symptoms of early CRPS type I through inhibition of sympathetic activity seems to be a paradoxic effect if one considers that this stage is typically characterized by sympathetic hypoactivity consisting of vasodilation, redness, warmth, and sweating. Possible explanations for this effect include blockade of afferent nerve fibers transmitting pain, blockade of efferent fibers eliminating sensitization of nociceptors, and inhibition of localized vasospasm.

Sympathetic blockade can be performed on the cervical sympathetic chain, primarily the stellate ganglion, for head, neck, and upper-extremity symptoms, and on the lumbar sympathetic chain for lower-extremity manifestations. For sympathetic blockade to be used as a therapeutic intervention, the following criteria should be met:

- The blockade should demonstrate a desired effect. Efficacy is assessed subjectively by the degree of pain relief and objectively by the degree of functional improvement of the extremity.
- The effect should last longer than the known duration of the local anesthetic.
- The patient must be willing to continue a series of sympathetic blockades for the therapy to be effective.

Once a sympathetic blockade has been shown effective, a series of frequent blocks is performed. Initially, the interval between procedures should roughly equal the time it takes for the pain to return and limit rehabilitation. This typically equates to intervals ranging from daily to no more than weekly. After the first three to five blockades, the time interval is extended to approximately 1.5 times the period of pain relief and improved function. Medical therapy, PT, and desensitization techniques are used in conjunction. As long as the patient's condition continues to improve, this therapy is continued. Resolution of symptoms typically occurs with four to eight blocks. If pain remains after sympathetic blockade, the diagnosis of CRPS type I should be reconsidered.

The patient's condition is considered refractory if pain relief is incomplete or if the painful condition returns after a series of sympathetic blockades has been performed.

1. **SGB.** It involves instillation of local anesthetic at the anterior tubercle of C6. These blockades are repeated one to three times a week, up to 10 in a series, until a long-term effect is achieved. If pain relief remains inadequate, a brachial plexus block or IV regional bretylium block is attempted. Cervical epidural block with a local anesthetic as well as a narcotic has been tried in a patient with CRPS from electrical injuries.
   a. **Indications.** CRPS type I and CRPS type II of the upper extremity are the two most common indications for SGB.
   b. **Complications.** Injections may result in Horner's syndrome and temporary hoarseness. Bilateral SGBs is not recommended because of possible bilateral recurrent laryngeal nerve paralysis and loss of cardioaccelerator activity. Phrenic nerve blockade results in temporary paralysis of a hemidiaphragm. Injections into the vertebral artery may result in seizures or cerebral air embolism. Intradural injections can result in unconsciousness, respiratory paralysis, seizures, and sometimes cardiovascular collapse. Other complications include brachial plexus dysfunction, pneumothorax, and osteitis of the transverse process.
2. **Lumbar sympathetic block.** The abdominal portion of the sympathetic trunk that supplies the lower extremities is anterolateral to the vertebral bodies of L1–3 along the medial margin of the psoas major muscle. Blockade of the lumbar sympathetic nerves can be performed with a spinal, epidural, or peripheral nerve block, but relief after lumbar sympathetic blockade most clearly delineates the cause of the pain as sympathetically mediated.
   a. **Indications** include sympathetically mediated pain, postherpetic neuralgia, phantom limb pain, and stump pain.
   b. **Complications** of lumbar sympathetic blockade include back pain, somatic nerve block, intraspinal anesthesia, intravascular injection, kidney trauma, and bowel perforation.
3. **IVRSB.** Bretylium, like guanethidine, selectively inhibits peripheral sympathetic nerve transmission by entering the preganglionic nerve endings by means of active transport and displacing norepinephrine from its storage sites. Its concentration builds up at these sites and prevents reuptake of norepinephrine and release of any remaining norepinephrine in response to neuronal stimulation. The norepinephrine depletion results in impairment and eventual loss of sympathetic adrenergic nerve function. This blockade lasts for many hours, for days, and sometimes for weeks because of the strong binding and slow elimination of the drug. In sufficient concentration, guanethidine can cause permanent damage to the norepinephrine reuptake pump. An IV regional blockade technique with **ketorolac** at a dose of 60 mg in saline solution or 0.5% lidocaine to volumes of 40 ml in the upper extremity and 50 ml in the lower extremity has produced prolonged pain relief with no serious side effects in some patients. IV regional blocks utilizing ketorolac and lidocaine produced only short-term pain reduction in patients with CRPS involving the lower extremity after four serial injections.
   a. **Indications.** IVRSB with bretylium or guanethidine remains an alternative for patients who do not respond to block procedures. This procedure is less invasive than blocks and can be performed by physicians unfamiliar with the use of regional anesthesia. It is also useful for patients for whom regional anesthesia is contraindicated.
   b. **Complications.** Placement of an Esmarch bandage and tourniquet on an extremity may be intolerable to a patient with painful CRPS type I. Agent not taken up by the tissue on release of the tourniquet may enter the systemic circulation and cause hypertension and tachycardia. Orthostatic hypotension can result from the chemical sympathetic blockade. Bretylium in high concentrations has local anesthetic and neuromuscular blocking properties. These drugs should not be administered to patients taking monoamine oxidase inhibitors or to patients with known pheochromocytoma. Other side effects include dysrhythmia, dizziness, diarrhea, edema, and nausea.

4. **IV anesthetic dose.** In patients with refractory CRPS, an almost complete resolution could be obtained with a combination of ketamine and midazolam infusion at anesthetic doses. Ketamine has reported to be successful orally as well, but further studies are recommended.

B. Dorsal column stimulation (DCS). If no response to conventional pharmacologic treatment is noted within 12 to 16 weeks, interventional techniques like spinal cord stimulation is recommended for refractory CRPS type I. The mechanisms of DCS are explained by the gate-control theory of pain and an increase in production of endogenous endorphins.

1. **Indications.** DCS is indicated for patients with chronic intractable pain. Patient-selection criteria include failure of conservative therapies, absence of drug abuse or history of psychological disorders, absence of contraindication to spinal implantation, and a successful trial of DCS with temporary electrodes.
2. **Complications** include infection, arachnoiditis, a high long-term failure rate, and mechanical failure.

C. Intraspinal opioid programmable pump. Preganglionic sympathetic intermediolateral columns of the spinal cord are modulated by projection from multiple supraspinal nuclei, including the nucleus raphae magnus. Intrathecal administration of morphine may be effective in relieving refractory CRPS type I by increasing nucleus raphae magnus inhibition of sympathetic outflow, in addition to its inhibitory effects on nociceptive neurons. Moreover, continuous intrathecal administration of morphine with a programmable pump allows stable CSF concentrations. The result is fewer episodes of pain breakthrough or drug overdose. Intrathecal therapy may also reduce the overall dosage requirements and delay the development of tolerance.

1. **Indications.** The intraspinal opioid programmable pump is reserved for treatment for patients with CRPS type I who are unresponsive to all other forms of less invasive measures. A successful trial of intrathecal morphine placed percutaneously is required.
2. **Complications.** An important disadvantage of an intraspinal opioid infusion pump is the high cost of implanting and maintaining the device. In addition, physical tolerance and dependence complicate therapy for many patients. Other problems include infection, arachnoiditis, mechanical failure, unremitting breakthrough pain, and opioid tolerance and dependence.

D. Surgical sympathectomy. For upper-extremity CRPS type I, surgical sympathectomy involves extensive ablation of the thoracic sympathetic ganglia from T1 to T6 or T7 through a transthoracic approach. Surgical sympathectomy for lower-extremity CRPS type I involves ablation of the lumbar sympathetic chain from L1 to L4. The pain relief derived from surgery may be inadequate or transient owing either to incomplete sympathetic denervation or to subsequent nerve regeneration.

1. **Indications.** Surgical sympathectomy usually is reserved for patients with CRPS type I who have been able to obtain definite but only temporary relief from repeated sympathetic nerve blocks and remain incapacitated by the disease.
2. **Complications.** Potential morbidity, including wound complications, permanent Horner's syndrome, and painful neuralgia, warrants exhaustive physical, pharmacologic, and psychological therapy before consideration of surgical sympathectomy.

V. REFERRALS

Patients with CRPS type I should be referred to a specialist in chronic pain treatment or a neurologist if

- signs and symptoms remain persistent despite a 6-week trial of conservative measures,
- pain is severe and intractable any time after the inciting event,
- a new-onset neurologic deficit is noted, or
- signs and symptoms have spread to other parts of the body.

Recommended Readings

Besson JM, Chaouch A. Peripheral and spinal mechanisms of nociception. *Physiol Rev*. 1987;67:67–186.

Bruehl S, Harden RN, Galer BS, et al. External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria. *Pain*. 1999;81:147–154.

Demangeat JL, Constantinesco A, Brunot B, et al. Three-phase bone scanning in reflex sympathetic dystrophy of the hand. *J Nucl Med*. 1988;29:26–32.

Eckmann MS, Ramamurthy S, Griffin JG. Intravenous regional ketorolac and lidocaine in the treatment of complex regional pain syndrome of the lower extremity: a randomized, double-blinded, crossover study. *Clin J Pain*. 2011;27(3):203–206.

Gobelet C, Waldburger M, Meier JL. The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy. *Pain*. 1992;48:171–175.

Kiefer RT, Rohr P, Ploppa A, et al. Complete recovery from intractable complex regional pain syndrome, CRPS-type I, following anesthetic ketamine and midazolam. *Pain Prac*. 2007;7(2):147–150.

Lee J, Nandi P. Early aggressive treatment improves prognosis in complex regional pain syndrome. Practitioner. 2011;255(1736):23–26.

Low AK, Ward K, Wines AP. Pediatric complex regional pain syndrome. *Pediatr Orthop*. 2007;27(5):567–572.

Lynch ME. Psychological aspect of reflex sympathetic dystrophy: a review of the adult and pediatric literature. *Pain*. 1992;49:337–347.

Mackey S, Feinberg S. Pharmacologic therapies for complex regional pain syndrome. *Curr Pain Headache Rep*. 2007;11(1):38–43.

Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150:971–975.

Nitzsche EU. Nuclear medicine imaging for diagnosis of CRPS I. *Handchir Mikrochir Plast Chir*. 2011;43(1):20–24. Epub 2011 Jan 11.

Rauck RL, Eisenach JC, Jackson K, et al. Epidural clonidine treatment for reflex sympathetic dystrophy. *Anesthesiology*. 1993;79:1163–1169.

Rommel O, Gehling M, Dertwinkel R, et al. Hemisensory impairment in patients with complex regional pain syndrome. *Pain*. 1999;80(1–2):95–101.

Rowbotham MC. Pharmacologic management of complex regional pain syndrome. *Clin J Pain*. 2006;22(5):425–429.

Sandroni P, Low PA, Ferrer T, et al. Complex regional pain syndrome I (CRPS I): prospective study and laboratory evaluation. *Clin J Pain*. 1998;14:282–289.

Sprague M, Chang JC. Integrative approach focusing on acupuncture in the treatment of chronic complex regional pain syndrome. *J Altern Complement Med*. 2011;17(1):67–70. Epub 2011 Jan 5.

Stanton-Hicks M, Janig W, Hassenbusch S, et al. Reflex sympathetic dystrophy: changing concepts and taxonomy. *Pain*. 1995;63:127–133.

Stanton-Hicks M. Complex regional pain syndrome: manifestations and the role of neurostimulation in its management. *J Pain Symptom Manage*. 2006;31(4 suppl):S20–S24.

Villanueva-Perez VL, Cerda-Olmedo G, Samper JM, et al. Oral ketamine for the treatment of type I complex regional pain syndrome. *Pain Pract*. 2007;7(1):39–43.

CHAPTER

52 Primary Central Nervous System Tumors

Edward J. Dropcho

More than 40,000 new cases of primary CNS tumors are diagnosed each year in the United States. Brain tumors are the second most frequent cause of cancer-related death among children. Brain tumors may affect adults at any age, and often have a devastating effect on patients and their families. This review will summarize the current clinical approaches to the most common primary brain tumors. For most if not all brain tumors the therapeutic strategies are in a state of evolution, and there are more than a few uncertainties and controversies. The past several years have seen an explosion of new knowledge of the molecular genetics and basic biology of brain tumors. Although the clinical progress seems painfully slow, these new discoveries are gradually being translated into more precise disease stratification and into targets for new therapies.

I. GLIOBLASTOMA AND ANAPLASTIC ASTROCYTOMA

A. Course of disease. The World Health Organization (WHO) stratifies malignant astrocytic neoplasms into two main groups, anaplastic astrocytoma (AA, WHO grade 3) and glioblastoma (GBM, WHO grade 4) based on the degree of hypercellularity, nuclear pleomorphism, mitoses, microvascular proliferation, and necrosis. GBM is the most common glioma in adults, accounting for 50% to 60% of all cases. Unfortunately, this tumor is also the most deadly. AA accounts for 15% to 20% of adult gliomas. There is a slight male predominance. Peak age incidence for GBM is approximately 55 years and for AA about 45 years. Recent epidemiologic evidence suggests an increasing incidence. Approximately 10% of patients with AA or GBM had a prior histologically proven diagnosis of astrocytoma or other lower-grade glioma.

Patients with GBM or AA generally present with a fairly short history of some combination of headache, seizures, and focal neurologic symptoms determined by the tumor location. Malignant gliomas appear on MR scans as an irregular mass lesion with heterogenous or ring enhancement (Fig. 52.1). There is a predilection to extend across the corpus callosum or to spread along other major white matter pathways. T2-weighted or fluid attenuated inversion recovery images typically show abnormal signal extending in an irregular shape for considerable distance beyond the margins of contrast enhancement. In most if not all patients there are infiltrating tumor cells within and beyond the area of abnormal T2/fluid-attenuated inversion recovery (FLAIR) signal. The variable topography and distance of tumor cell infiltration are serious obstacles to attempts at surgical resection or other "focal" therapies for these tumors.

B. Therapy. Standard treatment for patients with newly diagnosed GBM/AA is maximal tumor resection consistent with preservation of neurologic function, followed by limited-field radiation therapy (RT), and for most patients chemotherapy begun during or after RT. Several modern techniques facilitate the aggressive resection of gliomas and reduce the risk of neurologic morbidity for selected patients. Preoperative functional MRI, diffusion-tensor MRI, and intraoperative cortical and subcortical mapping can determine the tumor's proximity to and involvement of motor and speech structures. Intraoperative MRI allows the surgeon to assess the degree of resection and possibly continue the resection to remove more residual tumor.

For patients with symptomatic tumor mass effect, aggressive surgery usually improves neurologic function. Whether the extent of initial resection of GBM/AA has a major impact on survival continues to be controversial. There has never been and probably never will be a prospective randomized study in which patients are randomized to undergo differing degrees of tumor resection. Most (not all) retrospective studies show a survival

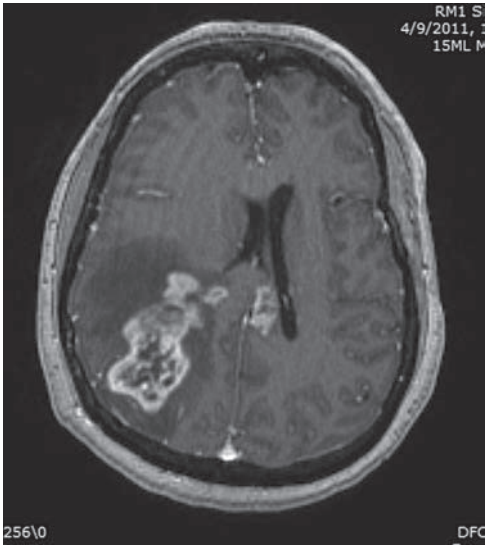

FIGURE 52.1 Axial T1-weighted MRI scan of a patient with a right parietal GBM, showing heterogeneous tumor enhancement, moderate surrounding cerebral edema and associated mass effect, and extension of tumor enhancement across the corpus callosum into the deep left hemisphere.

advantage for patients who undergo an "aggressive" resection. The cutoff value of how much of the enhancing tumor needs to be resected to impact survival ranges from 75% to almost 100% in various studies. In studies where multivariate analysis showed the extent of resection to be an independent prognostic factor, the impact on survival was nearly always less than that for patient age, tumor histology, and pretreatment performance status.

Standard postoperative RT for GBM/AA is 55 to 60 Gy "focal" or "limited-field" RT delivered to a target encompassing a 2 to 3 cm margin around the radiographically visible tumor area. GBM/AA occasionally spreads through the leptomeninges or recurs far from the initial tumor site, but for the vast majority of patients the ultimate cause of death is tumor recurrence within the initial RT target area. There is no evidence that higher doses of fractionated RT or a "boost" of stereotactic radiosurgery or brachytherapy in addition to conventional RT provide any survival advantage.

Based on a randomized prospective study, the current standard chemotherapy regimen for patients with newly diagnosed GBM is daily oral temozolomide taken concurrently during RT, followed by six or more monthly cycles of temozolomide after the completion of RT. Temozolomide is an alkylating agent that has excellent oral bioavailability and shows good penetration across the blood–brain barrier. Noncumulative myelosuppression is the dose-limiting toxicity. The efficacy of this chemotherapy regimen for patients with AA has not been definitively proven, but it is a common practice to administer the same treatment as for patients with GBM. For selected GBM/AA patients, another chemotherapy option is surgical implantation of BCNU-containing wafers at the time of initial resection.

Nearly all GBMs and AAs recur despite aggressive multimodality treatment. The median time to tumor progression after initial diagnosis of GBM is 6 to 9 months. For selected patients with relatively young age, good performance status, and accessible lesions, a second surgical resection can "set up" further chemotherapy, may improve neurologic function, and modestly prolongs survival. Depending on tumor size and location, some patients may benefit from single-dose or fractionated stereotactic radiosurgery. For many if not most patients with recurrent or progressive GBM or AA, further surgery or RT are judged not to be feasible or advisable. Systemic chemotherapy or other drug treatment is then the only option available. In the United States,

the most commonly used treatment for recurrent GBM/AA is bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor. In addition to its antiangiogenic and antitumor effect, bevacizumab is a potent antivascular permeability and anticerebral edema agent.

There has been intense interest in a growing number of drugs that have a cytostatic or cytotoxic effect on malignant gliomas by virtue of blocking or inhibiting growth factor receptors, intracellular or extracellular signaling pathways, angiogenesis, or tumor cell migration. To date, studies of these molecularly targeted agents for newly diagnosed or recurrent GBM/AA have unfortunately yielded disappointing results. Except for bevacizumab, none are currently used in standard therapy.

Supportive care for patients with GBM/AA includes varying doses of dexamethasone to reduce peritumoral edema and increase neurologic function, and aggressive treatment of pain and/or depression if they occur. The concepts and strategies for treating glioma-associated seizures are the same as those for treating localization-related epilepsy in general. There is no definite evidence that any particular antiepileptic drug is differentially effective for glioma-related seizures versus epilepsy caused by other structural brain lesions. For patients taking dexamethasone or receiving chemotherapy agents metabolized by the liver, the nonenzyme-inducing antiepileptic drugs (e.g., levetiracetam or valproate) may offer fewer drug interactions than enzyme-inducing drugs (e.g., phenytoin or carbamazepine). For patients who do not have seizures at initial presentation, there is no definite evidence to support long-term prophylactic antiepileptic drugs.

C. Prognosis. Patient age, tumor histology, and performance status are the most important prognostic factors for patients with malignant glioma. These are useful as predictors of individual patient outcome and are critically important in designing and interpreting clinical trials. With standard multimodality treatment, patients with GBM have a median survival of 12 to 18 months and only about 25% survive 24 months. Patients with AA have a median survival of 3 to 4 years.

Median survival is inversely proportional to age throughout all decades of adult life; older patients have a worse prognosis. Patients with a better performance status at the time of diagnosis have a better survival outlook than patients who present with severe neurologic impairment. Recent gene expression profiling studies have identified distinct molecular subclasses of GBM/AA, which may be associated with different survival outcome, but this is not yet part of standard clinical practice.

II. ASTROCYTOMA

A. Course of disease. Astrocytoma, oligodendroglioma, and mixed oligoastrocytoma together comprise 25% to 30% of all gliomas in adults. These "low-grade gliomas" should not be considered "benign" tumors, as they generally lead to a fatal outcome. Low-grade (WHO grade 2) astrocytomas are poorly circumscribed and are characterized by diffuse infiltration of atypical astrocytes with hyperchromatic nuclei. Gross and microscopic boundaries are difficult to define. Most tumors contain a mixture of cells with "fibrillary," "protoplasmic," or "gemistocytic" morphology. Expression of the intermediate filament glial fibrillary acidic protein (GFAP), as demonstrated by immunocytochemical staining, is a marker for astroglial derivation.

The median age at the diagnosis of supratentorial astrocytoma in adults is 35 to 40 years, which is significantly younger than for AA or GBM. There is a slight male predominance. Since the advent of MR scanning in the mid-1980s, at least 70% of patients with astrocytoma present with seizures and no headache or other neurologic symptoms. Astrocytoma usually appears as a poorly demarcated mass lesion hypointense on T1-weighted MR images and hyperintense on T2-weighted and FLAIR images. Gadolinium enhancement is present in 10% to 30% of cases. Infiltration of tumor cells nearly always extends beyond the margins of radiographically visible tumor.

B. Therapy. Few of the key issues regarding treatment for patients with low-grade astrocytoma have been studied in well-designed prospective or randomized clinical trials. It is therefore difficult to dogmatically state the "conventional" treatment for these tumors.

The proper treatment for patients needs to be individualized and based on several factors, including patient's age, clinical presentation, tumor size and location, and tumor histology.

The fact that MRI scanning identifies patients with astrocytoma early in their natural course raises the question of whether all patients require immediate treatment when the lesion is discovered. Currently, the unequivocal indications for early intervention for patients with a presumed or proven astrocytoma include neurologic signs and symptoms other than seizures; presence of significant mass effect on neuroimaging; growth of the lesion on serial scans; and patient age ≥50 years. It is unclear whether the presence of MRI contrast enhancement should be an indication of early treatment, assuming the area of enhancement is biopsied and shown to be histologically low grade. For younger patients with astrocytoma who have no neurologic symptoms other than seizures, it is reasonable to defer surgical resection or RT until clinical or radiographic tumor progression occurs. There is no clear evidence that deferring treatment in this subset of patients has a negative impact on overall survival or on the likelihood of malignant tumor transformation.

Surgical resection or RT are the main treatment options for astrocytoma. Surgery is rarely curative. The impact of the extent of surgical resection on patients' ultimate survival remains a matter of controversy. There has never been a prospective study in which "ideal candidates" with astrocytoma were randomly assigned to undergo varying degrees of surgical resection. Several retrospective series indicate a survival advantage for patients who underwent extensive surgical resection as compared with those who had only biopsy or "partial" tumor excision. In other series, the extent of surgery was not an independent predictor of survival. It is difficult to interpret these retrospective series because of a considerable selection bias: patients who have extensive resection are more likely to be younger, have better performance status, and have small, unilateral, relatively well-circumscribed tumors in noncritical locations than patients who have more conservative surgery.

There is also uncertainty whether all patients with astrocytoma should receive RT early in their course. In a large prospective multicenter study by the European Organization for Research and Treatment of Cancer (EORTC), patients with newly diagnosed astrocytoma (or oligodendroglioma) were randomized to either receive 54 Gy RT immediately after initial biopsy or resection, or to receive no RT until tumor progression. There was no difference in overall survival of patients who received early RT compared with patients in whom RT was deferred. There is no definite evidence that early RT benefits the subset of astrocytoma patients who undergo only biopsy versus surgical resection. Subsequent analysis of the EORTC study data showed a statistically significant prolongation in the time from initial diagnosis to tumor progression among patients who received early RT. These findings have been criticized for methodologic shortcomings because the study was not adequately designed to assess time to tumor progression as an endpoint.

If early RT for astrocytoma does not prolong survival but actually does delay tumor progression, it might be argued that early RT would delay tumor-related decline in patients' neurologic function. The counter argument is that RT itself can cause neurotoxicity and should therefore be delayed as long as possible. Long-term neurocognitive toxicity of RT is a significant concern for patients with low-grade gliomas, because at the time of initial diagnosis most patients are young, have mild or no neurologic deficits, and have an anticipated survival of at least several years. The few published studies of serial neuropsychological testing of "long-term" survivors show conflicting results as to whether RT causes significant neurocognitive deficits. Recent evidence suggests worsening neurocognitive function as patients are followed for many years after RT. The question of whether early RT is more likely to have a positive or a negative effect on patients' long-term neurologic function and quality of life is still unanswered.

C. Prognosis. In series published since the mid-1980s, the median survival of adults with supratentorial astrocytoma is 5 to 9 years. Patient's age at diagnosis is a strong independent predictor of outcome: time to tumor progression and overall survival are significantly shorter for older patients, particularly those over 50 years of age. Significant neurologic impairment at diagnosis has a negative impact on survival. Patients who present with a long history of seizures and no other neurologic deficits have a relatively

favorable prognosis. In some series, the presence of contrast enhancement on initial CT or MRI scans was predictive of shorter survival.

At the time of tumor recurrence or progression, 50% to 75% of initially low-grade astrocytomas will have undergone "malignant transformation" to AA or GBM. Malignant transformation of astrocytoma tends to occur sooner and more frequently among older patients than in younger patients. This histologic and phenotypic transformation reflects the acquisition of several genetic abnormalities. Unfortunately, it is not rare for astrocytomas that have remained stable for several years to eventually show progression leading to a fatal outcome. There does not seem to be a time point beyond which patients with astrocytoma can be confidently declared to be "cured" of their tumor.

III. OLIGODENDROGLIOMA

A. Course of disease. As with tumors of astrocytic derivation, oligodendrogliomas exhibit a spectrum of histologic malignancy. The WHO classification divides oligodendrogliomas and mixed oligoastrocytomas into two groups, low grade (grade 2) and anaplastic (grade 3). The classic histologic features of oligodendrogliomas are tumor cells with uniform round nuclei and clear perinuclear halos ("fried egg appearance"), with a "chicken wire" network of branching capillaries. Microcalcifications and microcystic spaces are common. The morphologic spectrum of oligodendrogliomas has been expanded to include tumors containing microgemistocytes or GFAP-expressing gliofibrillary oligodendrocytes. The presence of "significant" mitotic activity, microvascular proliferation, or necrosis defines an anaplastic oligodendroglioma. Median age of onset is 35 to 40 years for low-grade oligodendroglioma and around 50 years for anaplastic tumors. Mixed oligoastrocytomas contain some tumor cells with astrocytic morphology and other cells with oligodendrocytic morphology. The two elements are either spatially separate, or more often intermingled. Overall, low-grade and anaplastic oligodendrogliomas and oligoastrocytomas comprise about one-third of gliomas in adults.

As with astrocytomas, low-grade oligodendrogliomas present as seizures without other neurologic symptoms in at least 70% of patients. Anaplastic oligodendrogliomas or oligoastrocytomas present with some combination of seizures, headache, and focal neurologic symptoms. On MRI scans, low-grade oligodendrogliomas generally appear as an ill-defined nonenhancing lesion (Fig. 52.2A and B), whereas anaplastic tumors

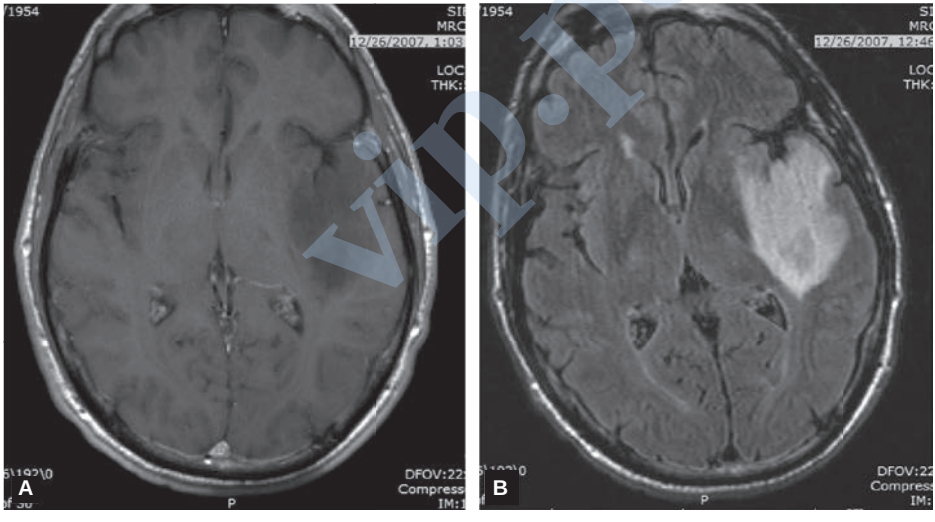

FIGURE 52.2 Axial MRI scan from a patient with a left temporal low-grade oligodendroglioma, showing no contrast enhancement on T1-weighted images **(A)** and diffuse hyperintensity on FLAIR images **(B).**

usually show heterogeneous or ring enhancement. Tumor calcifications are more frequent among oligodendroglial than among astrocytic tumors. Neither low-grade nor anaplastic oligodendrogliomas can be absolutely distinguished from astrocytic tumors based solely on neuroimaging characteristics.

B. Therapy. Treatment options for anaplastic oligodendroglioma or anaplastic oligoastrocytoma are similar to those for AA or GBM, including the maximal safe surgical resection followed by RT. As a group, oligodendrogliomas are more sensitive to chemotherapy than astrocytic tumors. Two prospective randomized studies of patients with newly diagnosed anaplastic oligodendroglioma showed that adding procarbazine/CCNU/vincristine chemotherapy (the PCV regimen) to surgery and RT significantly prolonged time to tumor progression but did not significantly prolong overall survival. Most patients in these studies who did not receive upfront PCV eventually received PCV or temozolomide at the time of tumor recurrence. Alternative options for patients with newly diagnosed anaplastic oligodendroglioma after biopsy or resection are RT only, temozolomide chemotherapy only, or combined RT plus temozolomide as is done for patients with GBM.

Many of the issues regarding management of patients with low-grade oligodendroglioma are similar to those for astrocytoma (see above). Low-grade oligodendrogliomas are generally more indolent than astrocytomas; for young patients who present with seizures and no other neurologic symptoms, it is reasonable to defer intervention until there is radiographic or clinical tumor progression. When intervention is deemed, necessary, patients should probably undergo the maximal surgical resection consistent with improved or preserved neurologic function. Early (vs. deferred) RT for low-grade oligodendroglioma does not prolong overall survival. Several nonrandomized studies have shown that chemotherapy (usually temozolomide) is effective in many patients with newly diagnosed or recurrent oligodendroglioma or oligoastrocytoma. The maximum radiographic response of oligodendroglioma to chemotherapy may not be seen for 8 to 12 months. Favorable response is associated with chromosome 1p/19q deletion, and with lower expression of the methylguanine methyltransferase DNA repair protein. There is no direct randomized comparison of chemotherapy versus radiation for low-grade oligodendroglioma, but chemotherapy is a reasonable alternative to RT in the hope of being able to defer RT and its risk of neurocognitive toxicity for as long as possible.

C. Prognosis. As with astrocytic tumors, younger age and good performance status are predictors of better outcome for patients with oligodendroglioma, independent of tumor grade. In recent published series, the median survival is 8 to 12 years for adults with low-grade oligodendroglioma and is 4 to 6 years for persons with anaplastic oligodendroglioma. Mixed oligoastrocytomas generally have a survival outcome intermediate between astrocytomas and "pure" oligodendrogliomas.

Two genetic changes in oligodendrogliomas have known prognostic significance. A chromosomal translocation resulting in codeletion of one copy of 1p and 19q is present in 60% to 75% of newly diagnosed low-grade oligodendrogliomas and about 50% of anaplastic oligodendrogliomas. A point mutation of the *IDH1* gene encoding isocitrate dehydrogenase occurs in at least two-thirds of low-grade and anaplastic oligodendrogliomas and oligoastrocytomas. The 1p/19q co-deletion and *IDH1* mutation usually coexist in the same tumor. Each is associated with improved survival independent of other prognostic factors.

IV. MENINGIOMA

A. Course of disease. The majority of meningiomas are asymptomatic and discovered incidentally by neuroimaging studies or at autopsy (see below). Symptomatic meningiomas are twice as common among women than men and account for approximately 20% of primary brain tumors in adults. There is a steadily increasing incidence above 20 years of age, with peak incidence during the seventh decade.

The WHO classification uses hypercellularity, nuclear pleomorphism, mitotic rate, focal necrosis, and infiltration of brain parenchyma to divide meningiomas into "benign" (grade 1, accounting for 85% of cases), "atypical" (grade 2, 5% to 15% of cases),

and "malignant" or "anaplastic" (grade 3, 1% to 5% of cases). There is a variety of histologic subtypes of meningiomas, including meningothelial, transitional, and fibrous; these subtypes generally do not have prognostic significance, except for more aggressive clinical behavior among the clear-cell, chordoid, rhabdoid, and papillary subtypes. Brain invasion is associated with a higher rate of tumor recurrence after therapy.

The clinical presentation of meningiomas is determined by their anatomic site. The most common sites of origin are along the cerebral convexity, parasagittal area and falx, and along the sphenoid ridge; together these sites account for at least two-thirds of cases. The slow growth of these tumors is reflected in the slow progression of signs and symptoms.

Meningiomas arise adjacent to dural surfaces and have a characteristic diffuse, homogeneous contrast enhancement on CT, or on MRI scans (Fig. 52.3). Calcification is present in at least one-third of cases. Peritumoral edema is variable and in some cases dramatic. Approximately 20% of patients have hyperostosis in the skull adjacent to the tumor; this bone is usually invaded by tumor cells. Approximately 5% of patients have two or more meningiomas at separate sites. The neuroimaging features of atypical or malignant meningiomas do not differ reliably from those of benign tumors. Arteriography or MR angiography/venography are frequently required to delineate the tumor's blood supply in consideration of surgery or preoperative embolization.

B. Therapy. Modern neuroimaging techniques have led to increased detection of incidentally discovered, asymptomatic meningiomas. Serial MRI scans in these patients usually show slow or no growth over several years. It is reasonable to defer surgery or other intervention, especially in elderly patients, unless symptoms develop or the tumor clearly enlarges.

The optimum treatment for symptomatic meningiomas is total surgical resection, if it can be done safely. The success (and morbidity) of aggressive surgery depends mainly on tumor location. Overall, gross total resection can be achieved in approximately 75% of patients. Tumors along the hemispheric convexity, anterior falx, or olfactory groove are most amenable to complete excision. For meningiomas arising in some anatomic locations such as petroclival, parasellar, cavernous sinus, or orbital tumors, gross total resection is often not possible without causing unacceptable neurologic morbidity.

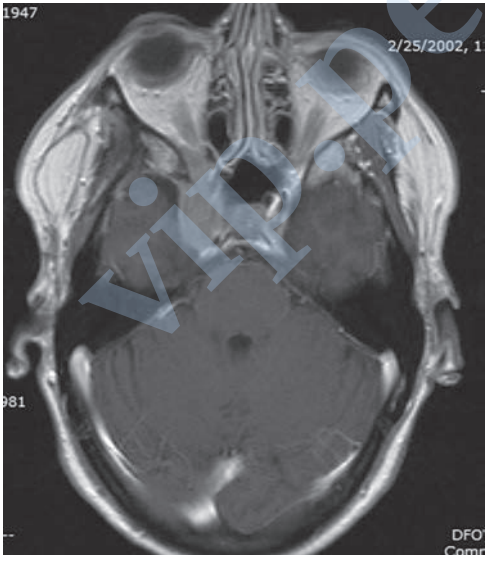

FIGURE 52.3 Axial T1-weighted MRI scan from a patient with a right parasellar meningioma, showing homogeneous contrast enhancement extending into the adjacent cavernous sinus and orbit.

Some patients with recurrent meningioma are candidates for a second surgical resection, depending on tumor size and location.

RT is not given following gross total resection of benign meningioma, but is generally recommended for patients with (1) symptomatic benign meningioma not amenable to aggressive surgical resection; (2) significant residual benign meningioma following attempted resection; (3) recurrent tumor following surgery; and (4) newly diagnosed atypical or anaplastic meningioma, regardless of the extent of initial surgical resection. Of these indications for RT, perhaps the most controversial is the group of patients with subtotally resected benign meningioma. The weight of retrospective data suggests a significantly lower long-term recurrence rate for these patients if they receive RT shortly after surgery.

RT options for meningioma include "standard" fractionated conformal RT, intensity-modulated RT, single-dose or fractionated stereotactic radiosurgery, interstitial brachytherapy, and proton beam therapy. Intensity-modulated RT, stereotactic radiosurgery, and proton beam therapy offer the theoretical advantage of being able to deliver a therapeutic dose to an irregularly shaped target, with reduced risk to nearby normal structures such as the optic pathways or brainstem. Published series report partial tumor shrinkage in 30% to 50% of patients and "tumor control" (stable or improved MRI scans) in up to 90% of patients, at least over a 5-year follow-up period. There are only a few studies that have determined control rates over 10 years or longer. Despite the common occurrence of meningiomas, there are virtually no prospective or controlled comparative studies of any RT approach or modality.

A significant proportion of patients with recurrent meningioma has tumors, which are not surgically resectable, have exhausted options for RT, and would therefore benefit from effective systemic treatment. Unfortunately, meningiomas are generally not sensitive to currently available chemotherapy agents. There are a few reports of partial response or prolonged tumor stabilization in patients with recurrent or anaplastic meningiomas treated with hydroxyurea, temozolomide, other chemotherapy regimens, tamoxifen, antiprogesterone agents, interferon-alpha, or somatostatin. To date, molecularly targeted agents such as the tyrosine kinase inhibitors imatinib or erlotinib have not shown significant efficacy.

C. Prognosis. The most important prognostic factors for meningioma are the extent of initial resection and the histologic tumor grade. Following gross total resection of benign meningioma, recurrence-free survival rates are close to 90% at 5 years, declining to 75% at 10 years, and 65% at 15 years. A high percentage of these patients never have tumor recurrence during their lifetime. Following subtotal resection alone, tumor recurrence rates at various time points are at least twice as high as for patients with gross total resection. Outcome is improved for patients who receive postoperative RT after incomplete resection.

Patients with atypical and malignant meningiomas clearly have a higher tumor recurrence rate and a shorter survival outlook than benign tumors. Approximately 50% of patients with atypical or malignant meningioma have tumor recurrence within 5 years of initial treatment. Reported median overall survival times vary between 2 and 10 years.

V. PRIMARY CNS LYMPHOMA

A. Course of disease. The great majority of primary CNS lymphomas (PCNSLs) occur sporadically in persons with no apparent immune deficiency. The incidence of PCNSL among immunocompetent persons has been increasing over the past 25 years, with a peak incidence between age 60 and 65 years. PCNSL accounts for about 3% of all primary brain tumors in adults. It is disproportionately common among patients with HIV infection, though the incidence has dropped dramatically with the advent of modern antiretroviral therapy. It may also occur in recipients of organ transplants or in persons with other iatrogenic immunodeficiency states.

More than 90% of PCNSLs are classified as diffuse large-cell B-lymphocyte tumors. The Epstein–Barr virus is detected in 90% of PCNSLs associated with HIV infection or organ transplants, but only rarely in sporadically occurring tumors.

The origin and pathophysiology of PCNSL in immunocompetent persons is poorly understood.

Patients generally present with a combination of altered mental status and focal neurologic symptoms. Neurologic deficits often progress rapidly and the diagnosis is usually made within 2 to 3 months. Seizures are less common than among patients with gliomas. PCNSL has a predilection for arising in deep or midline brain structures. On MRI scans, PCNSL characteristically appears as a bright fairly homogeneously enhancing mass lesion (Fig. 52.4). About one-half of patients have multifocal lesions. Lymphomatous infiltration of the posterior vitreous and/or retina (often asymptomatic) occurs in 10% to 20% of patients. Leptomeningeal dissemination occurs at some time in 10% to 40% of patients and is usually asymptomatic when present at the time of initial diagnosis.

B. Therapy. PCNSL is unique among primary brain tumors in that corticosteroids not only reduce peritumoral cerebral edema, but also have a direct oncolytic effect and can produce significant (but temporary) clinical and radiographic improvement. Whenever possible, steroids should be withheld prior to biopsy of patients with suspected PCNSL because their oncolytic effect may render the biopsy nondiagnostic.

Attempted surgical resection is of no benefit for patients with PCNSL. The only role for surgery is to provide diagnostic biopsy.

Patients with newly diagnosed PCNSL should have a staging workup including MRI of the brain and total spine, CSF exam (if safe) for cytology and flow cytometry studies, slit lamp ophthalmologic exam, CT scans of the chest and abdomen, serum lactate dehydrogenase, and HIV serology. IgH gene rearrangement analysis of CSF may show evidence for leptomeningeal tumor when other studies are negative or equivocal. It is not clear whether all patients should have a bone marrow biopsy and/or total-body FDG-PET scan.

High-dose intravenous (IV) methotrexate is the mainstay of treatment for PCNSL. When given in sufficient doses, methotrexate penetrates into the brain parenchyma regardless of the state of the blood–brain barrier and also produces cytotoxic concentrations in the CSF. The optimal methotrexate dose, schedule, and number of treatment cycles are not clearly known. For patients treated with high-dose IV methotrexate, upfront intrathecal chemotherapy is generally not recommended in the absence of definite radiographic or CSF evidence for leptomeningeal tumor. Several nonrandomized studies of high-dose methotrexate-based chemotherapy for PCNSL have shown radiographic complete responses in the majority of patients, and median survival of 3 years or more.

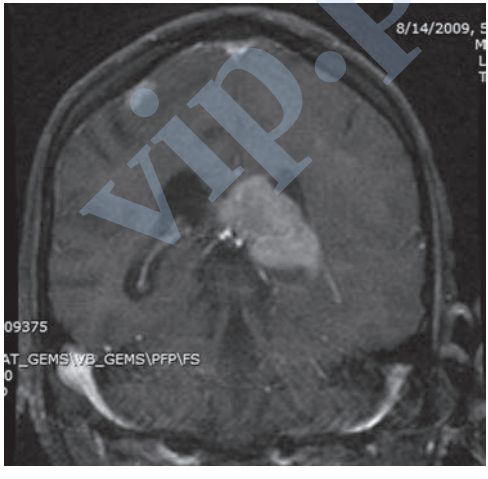

FIGURE 52.4 Coronal T1-weighted MRI scan from a patient with PCNSL, showing a large area of bright homogeneously enhancing tumor centered in the left thalamus, and a smaller focus of enhancing tumor in the superficial right frontal lobe.

High-dose IV cytarabine also achieves good brain and CSF concentrations. There are numerous published studies of multiagent regimens in which high-dose cytarabine, other chemotherapy drugs, or rituximab (an anti-CD20 monoclonal antibody) are added to high-dose methotrexate. Multiagent methotrexate-based regimens may yield longer progression-free survival than single-agent methotrexate therapy, but are generally more toxic, and have not been clearly shown to prolong overall survival. Other chemotherapy options for newly diagnosed PCNSL include high-dose chemotherapy with autologous stem cell rescue, or hyperosmolar disruption of the blood–brain barrier followed by a combination of intra-arterially and systemically administered drugs.

PCNSL is highly responsive to RT, but following RT alone the tumor recurs quickly and the median survival is only 12 to 18 months. Whole-brain RT (35 to 50 Gy) is generally given after the "induction" methotrexate-based chemotherapy. Whole-brain RT should be given to all patients who do not attain a complete radiographic remission (no contrast-enhancing tumor) following induction chemotherapy. It is less clear whether all patients who achieve a complete radiographic remission to initial methotrexate-based chemotherapy should then receive "consolidation" whole-brain RT. There are conflicting data whether consolidation RT necessarily extends overall survival in these patients versus deferring RT until the time of tumor recurrence. There is also concern over delayed neurotoxicity of PCNSL treatment: the risk of severe neurocognitive decline and leukoencephalopathy in survivors increases with patient age and among patients who receive methotrexate plus RT.

C. Prognosis. Younger age and good initial performance status are the two most important prognostic factors for survival outcome in PCNSL. There is a discrepancy between published median survivals of 3 to 4 years or more in studies of methotrexate-based chemotherapy versus median survivals of 12 to 18 months in population-based series. This may reflect a selection bias in which patients with better prognostic factors are entered into chemotherapy trials, and/or a less aggressive treatment approach in general community practice.

VI. MEDULLOBLASTOMA

A. Course of disease. Medulloblastoma is the most common malignant brain tumor of childhood, comprising 20% of brain tumors occurring before age 18 years. There is a bimodal incidence peak, at 3 to 4 years and 8 to 10 years of age, with a slight male predominance. About 20% of all medulloblastomas occur in adults, usually before age 30 years.

The WHO classification divides medulloblastomas into three main histologic groups. At least two-thirds of tumors have a "classic" histology, with sheets of "small, round, blue" tumor cells with hyperchromatic nuclei. The nodular/desmoplastic histologic pattern is present in 10% to 20% of cases and is disproportionately common in adults and in children under 3 years of age. The third histologic group shows severe anaplasia and/or large tumor cells, accounting for 5% to 20% of cases.

Medulloblastomas in children usually arise in or near the cerebellar vermis and fourth ventricle, and thus present with a combination of headache, vomiting (often occurring in the morning), lethargy, and gait ataxia. Tumors arising more laterally in the cerebellar hemisphere present with ipsilateral ataxia, with or without signs and symptoms of increased intracranial pressure. Tumor enlargement or invasion into the brainstem cause cranial nerve palsies and long-tract findings. The diagnosis is usually made within 2 to 3 months of symptom onset.

Medulloblastoma is the primary brain tumor most likely to disseminate in the subarachnoid space and is also the brain tumor most likely to metastasize outside the CNS, usually in the setting of recurrent disease at the primary site.

On MRI scans, medulloblastoma usually appears as a homogeneously or heterogeneously enhancing mass filling and distorting the fourth ventricle. The tumor may be centered more laterally in the cerebellar hemisphere (Fig. 52.5). Calcifications or hemorrhage may be present. Hydrocephalus is present in at least 75% of cases at diagnosis.

B. Therapy. Multimodality treatment for medulloblastoma includes aggressive surgical resection, followed by "risk-adapted" RT and chemotherapy. Gross total resection can

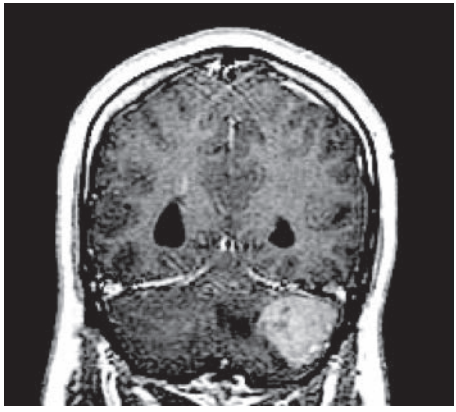

FIGURE 52.5 Coronal contast-enhanced T1-weighted MRI scan from a young man with a desmoplastic medulloblastoma in the left cerebellar hemisphere.

be performed in approximately 75% of patients. One-half of patients require placement of a permanent CSF shunt. Postoperatively, children are clinically stratified into "average-risk" and "high-risk" prognostic subgroups based the extent of initial surgical resection and the presence or absence of leptomeningeal dissemination. Average-risk patients (about two-thirds of the total) have a gross total or nearly gross total tumor resection, negative CSF cytology, and no leptomeningeal spread on brain and total spine MRI scanning. Patients are high-risk if they have a less complete tumor resection, and/or evidence for leptomeningeal dissemination at diagnosis.

Average-risk children older than 3 years of age receive RT to the craniospinal axis (23 to 25 Gy), plus a higher RT dose to the tumor site (55 Gy), and posterior fossa (36 Gy). Multiagent chemotherapy (usually including cisplatin, cyclophosphamide, and vincristine) is given for several months after RT.

Children over the age 3 years with high-risk disease also receive postoperative RT, usually at a higher craniospinal axis dose than average-risk patients. There is a general strategy to give more intensified chemotherapy regimens to high-risk than to average-risk children, though there is no clear evidence establishing the best approach.

Children < 3 years of age have a higher incidence of leptomeningeal dissemination at diagnosis. The risk of severe neurocognitive toxicity in survivors is much higher if RT is given early in childhood, so these patients generally receive intensive chemotherapy regimens after surgery with the goal of obviating or at least deferring RT for as long as possible.

Following tumor resection, adults with medulloblastoma are stratified into average-risk and high-risk groups as are older children, and treated with RT and chemotherapy accordingly. Adults tend to tolerate the multiagent "childhood medulloblastoma" chemotherapy regimens less well than do children.

C. Prognosis. The most frequent mode of treatment failure is recurrence in the posterior fossa, with or without leptomeningeal dissemination. In modern series which include chemotherapy as part of multimodality treatment, the 5-year progression-free survival rate for older children with average-risk disease is 80% or more. The majority of these children are cured. The 5-year progression-free survival rate is 40% to 70% for older children with high-risk disease, and 30% to 50% for children < 3 years of age. Large cell/anaplastic medulloblastomas generally carry a worse outcome. The nodular/desmoplastic variant in young children is associated with better survival outcome. Metastatic disease at diagnosis carries a worse prognosis at any age. The present clinical staging scheme is not able to identify which average-risk patients are more likely to develop tumor recurrence and therefore require more aggressive initial treatment, nor to identify which patients could be cured with less aggressive treatment (especially the dose of craniospinal RT) so as to reduce the incidence and severity of long-term treatment

sequelae. In recent gene expression profiling studies, medulloblastomas fall into 4 or 5 groups with differing molecular genetics and somewhat different (though overlapping) representation of patient age, gender, and tumor histology. It is hoped that molecular subtyping will further refine the current clinical patient staging and help to individualize therapy.

The relatively favorable survival outcome and potential curability of medulloblastoma are tempered by significant treatment sequelae in the majority of survivors. About 25% of children develop the "cerebellar mutism syndrome" within a few days after surgery. This consists of mutism, axial hypotonia, ataxia, and irritability. Patients eventually recover, but one-half of severely affected children have long-term speech, motor, and cognitive deficits. Survivors of childhood medulloblastoma have a high incidence of other long-term sequelae, including growth failure and other neuroendocrine dysfunction, neurocognitive deficits which may be progressive, requirement for special education, behavioral disorders, and the risk of second neoplasms including meningioma and glioma. Toxicities are more common and more severe among children treated at a younger age.

Recommended Readings

Bromberg JE, van den Bent MJ. Oligodendrogliomas: molecular biology and treatment. *Oncologist*. 2009;14:155–163.

Campbell BA, Jhamb A, Maguire JA, et al. Meningiomas in 2009: controversies and future challenges. *Am J Clin Oncol*. 2009;32:73–85.

Crawford JR, MacDonald TJ, Packer RJ. Medulloblastoma in childhood: new biological advances. *Lancet Neurol*. 2007;6:1073–1085.

Morris PG, Abrey LE. Therapeutic challenges in primary CNS lymphoma. *Lancet Neurol*. 2009;8:581–592.

Pfister SM, Korshunov A, Kool M, et al. Molecular diagnosis of CNS embryonal tumors. *J Neuro-oncol*. 2010;120:553–566.

Schiff D, Brown PD, Giannini C. Outcome in adult low-grade glioma: the impact of prognostic factors and treatment. *Neurology*. 2007;69:1366–1373.

Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10:459–466.

van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet*. 2005;366:985–990.

Wen PY, Kesari S. Malignant gliomas in adults. *N Engl J Med*. 2008;359:492–507.

CHAPTER

53 Nervous System Complications of Cancer

Jack M. Rozental and Jeffrey J. Raizer

Neurologic complications of cancer can be metastatic, treatment related, or remote (paraneoplastic). They can cause neurologic disability or death, even while systemic disease is under control. Timely recognition and management of some complications can have a beneficial effect on quality and length of life. In most instances, management of nervous system complications is palliative. Thus, quality-of-life judgments may be more important than longevity in making therapeutic decisions.

I. METASTASIS TO THE BRAIN PARENCHYMA

A. About 20% of cancer patients develop metastases to the CNS, but only one half are symptomatic. Metastases are the most common CNS tumors (approximately 170,000 per year).

1. Seventy-five percent of brain metastasis are from lung (50%), breast (15%), and melanoma (10%); gastrointestinal, gynecologic, urologic, and cancers of unknown primary cause another 10%.

2. Twenty-five percent of metastatic lesions are single; about 20% of patients have two metastatic lesions.

3. Patients with gastrointestinal, gynecologic, or urologic tumors tend to have single brain lesions; approximately 50% are to the posterior fossa. Only 10% of other tumors metastasize to the posterior fossa.

4. Patients with lung cancer, melanoma, and tumors of unidentified origin usually have multiple metastatic lesions.

5. Most metastases localize to the frontal and parietal lobes (because of their relative mass and higher blood flow) and a few (1%) to the brainstem. Metastases lodge at the arterial border zones of the major cerebral vessels because of decreased vascular caliber and flow; hence, their preference for the gray–white junction.

6. The tumors most likely to bleed are melanoma, renal, and thyroid—the most vascular.

B. In up to 10%, an intracranial mass in patients with cancer is not a metastasis. The differential diagnosis includes:

1. Primary CNS tumor.

2. Brain abscess.

3. Demyelinating plaque.

4. Arteriovenous malformation.

C. Management.

1. Increased intracranial pressure (ICP) from a metastasis is usually managed with a bolus of dexamethasone 10 mg intravenously (IV) followed by 16 mg IV or orally in divided doses for maintenance.

2. For patients with minimal neurologic deficit no bolus is needed

3. If needed, dexamethasone is increased by 8 or more mg IV or orally four times a day.

4. Clinical improvement should be apparent within 24 to 48 hours of treatment, continue for several days, and then plateau.

5. Dexamethasone is tapered as tolerated after the patient's condition is stable and more definitive therapy has started. The goal is to maintain optimal neurologic function on the lowest steroid dose due to the large number of side effects.

6. A proton pump inhibitor or H2 blocker may be started as prophylaxis against gastric bleeding, ulceration, or perforation.

D. Patients in extremis from increased ICP may need an osmotic diuretic, e.g., mannitol 20% solution 1 g per kg IV.

1. Smaller doses of mannitol (0.25 to 0.5 g per kg) can be repeated, but ICP must be monitored.

2. Only short-term hyperosmolar therapy is useful because:
   a. when serum sodium increases to >160 mEq per L, treatment is no longer useful,
   b. dehydration can lead to cardiovascular collapse, and
   c. a rebound increase in ICP occurs despite continued treatment, especially upon rehydration.
3. Patients given osmotic diuretics need bladder catheterization.

E. Hyperventilation and **osmotic diuretics** are used only if a definitive end point is first established, because beneficial effects are temporary. The target of hyperventilation is a pCO_2 of 30 to 35 mm Hg (see Chapter 58).

F. Seizures.

1. Between 15% and 30% of patients with brain metastases have seizures.
2. Status epilepticus is managed in the standard manner (see Chapters 38 and 39).
3. Prophylactic antiepileptic drugs (AEDs) can be considered for patients with melanoma (50% of whom have seizures); otherwise there is no role for them. Posterior fossa metastases are not epileptogenic.
4. When phenytoin, dexamethasone, and whole-brain irradiation are used concurrently, the risk of erythema multiforme and erythema multiforme bullosa (Stevens–Johnson syndrome) increases.
5. Given the frequency of drug–drug interactions with older AEDs, newer agents should be considered first.

G. Surgical management.

1. The ideal candidate has minimal disability, a single, circumscribed, accessible lesion, and controlled systemic disease.
2. A shunt is indicated for obstructive hydrocephalus.
3. Current areas of controversy include:
   a. **Reoperation.** A second resection may be considered for a lesion that recurs in the original tumor bed with minimal further parenchymal invasion.
   b. **Excision of multiple metastatic masses.** If one or two of several metastatic lesions are symptomatic or life-threatening, palliative resection should be considered.

H. Radiation therapy (RT).

1. RT is the primary therapy for brain metastasis.
   a. Standard dosage is 30 Gy to whole brain over 10 days; alternative dose-fractionation schedules are used in some cases.
   b. Patients with radio-resistant tumors (melanoma and renal cell) may benefit from a radiosurgical boost to the tumor bed (section 3).
   c. If dexamethasone is administered, acute complications of RT are few (mild headache, fatigue, hair loss, and asthenia).
   d. CNS tolerance to RT is inversely proportional to the volume irradiated and dose used. Toxic effects include:
      (1) **Acute encephalopathy:** headache, nausea, and changes in mental status from increased ICP. Occurs within a few days and is common if steroids are not used during RT. Steroids in high doses help.
      (2) **Early delayed encephalopathy:** probably from demyelination; starts 14 to 120 days after RT with headache and drowsiness or brainstem dysfunction—ataxia, diplopia, and dysarthria. Spontaneous recovery in a few weeks is usual but steroids can help.
      (3) **Delayed radiation encephalopathy:** occurs months to years after RT. It manifests as diffuse cerebral atrophy, focal deficits, increased ICP, or as a normal pressure hydrocephalus (NPH) like syndrome (see Chapter 8). Pathology reveals necrosis—either from direct RT damage or vascular changes such as microangiopathy or accelerated atherosclerosis. A VP shunt is sometimes helpful.
      (4) **Delayed radiation necrosis:** usually occurs >1 year after RT; it can look and behave like a tumor.
      (5) **Myelopathy:** occurs within the first year of RT from demyelination and is usually transient.
      (6) **Delayed severe myelopathy:** occurs >1 year after RT from necrosis or atrophy, resembles cord compression with para- or quadriplegia but no pain. MRI is often normal. No specific treatment exists but steroids may help temporarily.

(7) **Plexopathy:** RT-induced plexopathy can occur early but is usually delayed and must be differentiated from direct involvement of the plexus. Clues to RT damage include doses >60 Gy, painless weakness, lack of lymphedema or induration of the supraclavicular fossa, and presence of myokymic discharges on electromyography (EMG).

2. **Prophylactic cranial irradiation** is standard of care for limited stage small-cell lung cancer (SCLC); although it decreases the incidence of subsequent brain metastasis, it does not significantly affect patient survival.
3. **Stereotactic radiosurgery (SR) or Gamma Knife** delivers a single large or several smaller RT fractions to a well-defined, limited intracranial target with a sharp peripheral dose fall-off and minimal exposure to normal surrounding brain.
   a. A 10 to 24 Gy fraction can be administered before or after conventional RT to tumor diameters of about 3 cm.
   b. To remain within brain tolerance parameters, doses vary inversely with tumor size and the number of isocenters.
   c. Local tumor control rates >80% can be achieved especially with radioresistant tumors, with complete response rates of approximately 40%.
   d. Tumors <2 cm may respond better than larger ones and the risk of radiation necrosis is also less.
   e. For patients with a single lesion, SR after whole-brain RT is beneficial. SR without whole-brain RT is controversial as local and distant brain control decreases but survival is unchanged.
4. A patient with **radiation necrosis** has acute or subacute neurologic deterioration and signs and symptoms of a mass lesion.
   a. Neither CT nor MRI can help differentiate a necrotic mass from recurrent tumor. However, MR spectroscopy, MR perfusion, or PET imaging may.
   b. Necrosis can be managed conservatively with steroids; recent data suggest using bevacizumab.
   c. Resection is indicated if neurologic deterioration continues, escalating steroid doses become necessary, or intolerable steroid toxicity develops.

I. Chemotherapy.

1. As most tumors are drug-resistant, chemotherapy is not routinely indicated for management of CNS metastasis.
   a. CNS metastases most frequently occur in patients with advanced, unsuccessfully treated cancers. Breast cancer patients who are Her-2 positive often have limited or no systemic disease but have CNS disease because trastuzumab cannot penetrate the CNS.
   b. The blood–brain barrier may hinder penetration of most agents; hence, the CNS relapses.
2. Chemotherapy may be considered in
   a. Patients with a chemosensitive tumor, good performance status, and inactive systemic disease with a metastasis that recurs after RT with or without surgery.
   b. CNS metastasis from SCLC, breast, lymphoma, and germ cell tumors may respond to chemotherapy at rates comparable with those of the systemic tumor.

J. Cerebellar metastasis.

1. Common symptoms include: gait or limb ataxia, nystagmus, papilledema, headache, dizziness, vomiting, and double vision.
2. Initial treatments are the same as for supratentorial metastases: dexamethasone and RT.
3. Acute complications of RT are more common with cerebellar than with supratentorial metastases. Therefore, dexamethasone is started 48 hours prior to RT.
4. The risk of brain herniation after lumbar puncture (LP) is greater in patients with posterior fossa masses.
5. The indications for resection are the same as for supratentorial metastases, but any sign of clinical instability or deterioration, an expanding mass, hydrocephalus, or lack of response to dexamethasone should prompt consideration of immediate neurosurgical intervention except in brain stem lesions.
6. After resection of a cerebellar metastasis, patients have a higher incidence of developing leptomeningeal dissemination due to the proximity of the tumor to CSF spaces.

II. PITUITARY APOPLEXY

A. *Pituitary apoplexy is an emergency*. Acute panhypopituitarism occurs when a metastasis in the sella turcica or the pituitary gland necroses or hemorrhages—causing headache, ophthalmoplegia, bitemporal hemianopsia, blindness, encephalopathy, coma, hypotension and signs of meningeal irritation.
B. Treatment is with high IV doses of corticosteroids; surgical decompression may be needed.
C. Complete endocrine work up is indicated as hormone replacement will be needed.

III. METASTASIS TO THE SKULL BASE

The hallmark of metastasis to the skull base is involvement of the cranial nerves (CN). Most tumors arise from the breast, lung, or prostate. Five major syndromes have been recognized.

A. Orbital syndrome characterized by dull, continuous, progressive pain over the affected eye with proptosis, external ophthalmoplegia, and blurred vision. There is decreased sensation over the distribution of ophthalmic division of the trigeminal nerve (CN V).
B. Parasellar syndrome (cavernous sinus metastasis) manifests as unilateral frontal headache and ophthalmoplegia. Patients may have decreased sensation over the distribution of the ophthalmic division of CN. V. If cavernous sinus thrombosis occurs, there may be chemosis, edema of the eyelids and forehead, proptosis, and papilledema with retinal hemorrhages. In both the parasellar and orbital syndromes, steroids are warranted before RT to prevent acute vision loss from radiation-induced edema.
C. Middle fossa syndrome (Gasserian ganglion) is characterized by pain, numbness, or paresthesias over the distribution of the second (maxillary) or third (mandibular) divisions of CN V. The initial presentation may be a "numb chin" or a "numb lip." Pterygoid and masseter weakness and abducens palsy occur late. About 65% of these lesions are from breast cancer and 15% from lymphomas. Approximately half the patients have mandibular metastasis, 15% have skull base lesions, and 20% carcinomatous meningitis.
D. Jugular foramen syndrome manifests as hoarseness and dysphagia (CN X) with or without pain (CN IX or X). Examination may show asymmetric palatal elevation (CN IX), weakness of the ipsilateral sternocleidomastoid and trapezius muscles (CN XI), and Horner's syndrome (oculo-sympathetic). Weakness and atrophy of the tongue may be found if the tumor extends to the adjacent hypoglossal canal (CN XII).
E. Occipital condyle syndrome manifests as stiff neck and severe occipital pain that increases with neck flexion. Dysarthria and dysphagia from unilateral involvement of CN XII are seen in approximately 50%.

IV. DURAL METASTASIS

Dural metastases can cause headache or underlying venous sinus thrombosis and may invade the parenchyma. Malignant subdural effusions can also occur. Breast and prostate tumors are most commonly implicated.

V. SPINAL EPIDURAL METASTASIS

A. Metastatic epidural spinal cord compression (ESCC) occurs in approximately 5% to 10% of patients with cancer. *ESCC is an emergency*.
B. Prognosis. The most important determinant is neurologic function at presentation.
1. Ninety percent of ambulatory patients remain so after treatment, and have a 75% probability of surviving 1 year. Fewer than 10% of nonambulatory patients survive 1 year.
2. Only 50% of paraparetic and 13% of paraplegic patients with "radiosensitive" tumors become ambulatory after treatment.
3. Once neurologic dysfunction begins, paraplegia and loss of sphincter control occur within hours and are usually irreversible.

C. ESCC must be suspected on clinical grounds and must prompt timely confirmation and treatment.
1. About 60% of epidural metastates are from prostate, lung, breast, and kidney cancer; about 15% from **multiple myeloma.**
2. Approximately 50% of adults with an acute transverse myelopathy have metastatic ESCC. In 50% it is the initial manifestation of cancer, and in one half of those, the primary is lung cancer.

D. **Presentation.**
1. About 95% of patients with epidural tumor have progressive axial **pain** with or without a radicular or referred component.
2. Some weakness and sensory disturbance are present in 80% of patients.
3. Almost 60% of patients have sphincter dysfunction, a poor prognostic sign that implies bilateral cord or root damage.

E. **Site of involvement.**
1. The vertebral column, and never the intervertebral disks, is involved in about 85% of epidural tumors from solid cancers.
   a. The vertebral body is involved in 45%.
   b. The posterior arch and pedicle are involved in 40%.
   c. The entire vertebra is involved in 15%.
2. About 50% to 70% of lesions involve the thoracic spine.
3. About 20% to 30% involve the lumbosacral spine.
4. About 10% to 20% involve the cervical spine.
5. At least one-third of patients with breast and prostate cancer have metastatic lesions at multiple levels.

F. There are **three potential mechanisms of metastatic ESCC.**
1. Most common is hematogenous spread to the vertebra.
2. The valveless veins in Batson's plexus allow tumor seeding when the intraabdominal pressure increases.
3. Direct invasion of a paravertebral mass through the intervertebral foramen occurs in 75% of ESCC from lymphoma.

G. **Diagnosis.** Non-contrast-enhanced followed by contrast-enhanced MRI should be performed in all cases of suspected ESCC to establish the diagnosis and the extent of tumor invasion (Fig. 53.1). Because disease is often multifocal and discontinuous, the entire spine should be imaged. CT scan with or without myelography may be needed if an MRI is contraindicated.

H. **Initial management.**
1. If spinal cord compression is suspected, or upon confirmation, a 10-mg IV bolus of dexamethasone is administered and followed by 4 mg IV every 6 hours. If pain is severe, or if there is paresis or sphincter involvement, a 100-mg IV bolus of dexamethasone is administered and followed by 24 mg IV every 6 hours until more definitive treatment is started.
2. Maintenance dosage of dexamethasone (4 mg IV or orally every 6 hours) is then tapered as tolerated.
3. Steroids can promote clinical improvement and decrease pain but rarely produce a dramatic reversal of established neurologic disability. Prognosis is better when they do.
4. An indwelling bladder catheter should be inserted to check PVR and remain in.
5. Deep venous thrombosis prophylaxis and a stool-softening regimen should be started.

I. Although the intent of therapy remains **palliative,** several treatment options are available.
1. **Surgery is indicated for establishing a diagnosis, in cases of spinal instability and/or presence of bone fragments within the spinal canal or continued neurologic decline during RT.**
2. **Decompressive laminectomy** works only temporarily. It fails because
   a. Metastatic tumor is generally located in the vertebral body (anterior to the spinal cord) and not in the neural arch.
   b. **Laminectomy** may contribute to spinal instability.
3. **Anterior vertebral body resection**
   a. This must be coupled with surgical stabilization of the spine.
   b. Operative morbidity (10%) is from non-healing, breakdown, or infection of the wound and failure to stabilize the spine due to bone metastases.

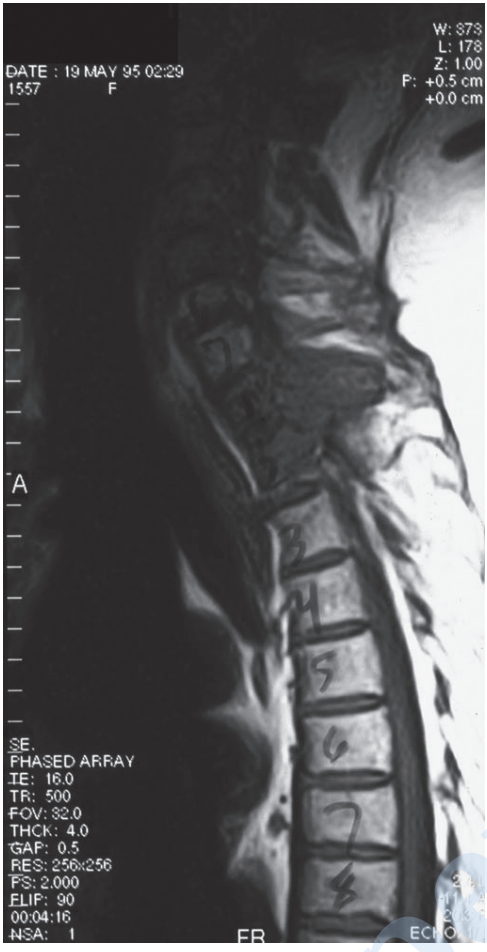

FIGURE 53.1 Sagittal MRI of the spine in a patient with metastatic ESCC. (Courtesy of José Biller, MD.)

4. **RT** alone is the procedure of choice for radiosensitive tumors.
   a. A total dose of 20 to 40 Gy divided over 10 to 20 fractions is the usual treatment—30 Gy is the most common dose.
   b. The port should encompass two vertebral bodies above and below the epidural defect and any discontinuous lesions.
   c. RT is indicated promptly after the diagnosis is made and should follow administration of dexamethasone.
   d. If surgery is performed first, RT should follow after the wound heals.
   e. The tumors that most commonly produce ESCC—lung, breast, prostate, and lymphoma—are likely to respond to RT.
   f. If neurologic deterioration continues, surgical intervention should be considered.
   g. The complications of RT are:
      (1) Myelosuppression.
      (2) Radiation myelopathy or syrinx (6 to 18 months after therapy).
      (3) Risk of a subacute syndrome characterized by Lhermitte's sign several weeks after radiation.
5. **Laminectomy plus radiation.** For select patients, surgery followed by RT is better than RT alone for preserving function and increasing survival.

6. **Epidural tumors** do not respond rapidly enough to chemotherapy to warrant its use in most acute situations.
7. **Recurrent ESCC.**
   a. **Local metastatic lesions** develop within two vertebral bodies of a previous lesion and within 3 months of the original diagnosis. They represent a failure of tumor control at the margin of the radiation port.
   b. **Distant metastatic lesions** develop three or more vertebral bodies from a previous lesion and 15 months or longer after the original diagnosis.
   c. Patients who previously responded to RT may be considered for repeat RT; they may benefit but not survive to experience the necrotizing consequences of exceeding spinal cord radiation tolerance.
   d. Stereotactic body radiotherapy is being used more frequently for recurrent tumors and sometimes initially due to the focal nature of the treatment, thereby minimizing toxicity to the neural structures.

VI. LEPTOMENINGEAL METASTASIS

A. Leptomeningeal metastasis (LM) occurs when tumor cells invade the arachnoid and pia mater, focally or multifocally.
1. They develop in as many as 70% of patients with leukemia, and in 5% to 8% of patients with non-Hodgkin's lymphoma. CNS lymphomas often involve the leptomeninges. Among solid tumors, breast is the most common, followed by lung, gastrointestinal tract, and melanoma.

B. **Pathology.** Typical pathologic features are:
1. Sheetlike layers and clumps of tumor cells ("lumpy-bumpy disease").
2. Infiltration of cranial or spinal nerve roots.
3. Parenchymal invasion through the Virchow-Robin spaces.

C. **Presentation.**
1. Clinical features reflect the level of CNS involvement, alone or in some combination. Multifocal neurologic symptoms in a cancer patient is LM until proven otherwise.
2. The initial feature may be hydrocephalus.
3. New, worsening, unremitting headaches or somatic pain that present without apparent cause.
4. Extraocular, or any other cranial nerve palsies (see Chapter 12).
5. Involvement of lumbosacral nerve roots may cause a **cauda equina syndrome.**
6. Major differential diagnoses include bacterial, fungal, tubercular, or granulomatous meningitides.

D. **Diagnosis.**
1. **LP** should be performed in all cases where MRI is not diagnostic and there is no risk of herniation. Results are abnormal in >95% of cases.
2. LP may show lymphocytic pleocytosis, low to very low glucose, elevated protein, or malignant cells. The CSF pressure may be elevated.
3. Cytology is positive in only 50% on the first LP, so two to three may be needed. Cytology should be performed on a cytospin sample (not on stained smears) processed immediately after withdrawal to prevent cell lysis.
4. Markers such as carcinoembryonic antigen, CA27.29, PSA, β_2 microglobulin, and lactate dehydrogenase can be used for follow-up evaluation of the CSF, once initial cytologic diagnosis has been made.
5. **Gadolinium-enhanced MR** images show enhancement on the surface of nerve roots, spinal cord, CN, cerebellar folia, or over the cerebral convexities; fluid-attenuated inversion recovery (FLAIR) sequence may also provide evidence of LM. MRI may be abnormal even without positive cytology or spinal symptoms. Treatment can be initiated on the basis of MRI findings.

E. **Initial treatment.**
1. The systemic disease status and likelihood of successful palliation should be considered in the decision to treat.
2. Dexamethasone rarely provides symptomatic improvement and should be tapered after more definitive treatment is initiated.

F. Craniospinal or local RT.

1. Usual doses are 30 Gy to the entire neuraxis or 24 to 30 Gy to the most symptomatic areas.
2. Most patients are unable to tolerate RT to the entire neuraxis; it rarely controls LM and it produces myelosuppression. Craniospinal RT is reserved mainly for meningeal leukemia.
3. Local RT is indicated at the level of a radiographic or functional spinal block, especially if Intrathecal (IT) treatment is considered.

G. IT chemotherapy.

1. This modality is useful because tumor diffusely infiltrates the leptomeninges.
2. After systemic administration, most drugs reach CSF concentrations between 1% and 25% of the plasma concentration. Hence, the dose intensity of treatment in the CSF is decreased, predisposing to CNS failure. Some drugs like methotrexate (MTX) and cytarabine (cytosine arabinoside) have good CNS penetration and may provide adequate drug distribution to the CSF if administered IV in high doses.
3. Because the volume of distribution in the CSF is small, high concentrations can be achieved with small IT drug doses.
4. Drug clearance half-lives tend to be longer in the CSF than in plasma, maximizing exposure.
5. IT chemotherapy may be used alone or with neuraxis RT.
6. The first few doses can be administered by means of LP, but if continued, this can lead to an epidural hematoma, CSF leaks, and virtual subdural or epidural compartments through which drug can be lost.
7. Other constraints to delivery through LP relate to the dynamics of CSF flow, which is craniocaudal, tends to bypass the ventricles, is affected by patient position, may be severely disturbed in the presence of meningeal tumor with or without increased ICP and cannot be done with low platelets.
8. A ventricular catheter with a subcutaneous (Ommaya) reservoir should be implanted for more optimal drug delivery.
   a. Infections are a serious but rare complication of Ommaya reservoirs; proper sterile technique should be followed with each use.
   b. Fever, headache, lethargy, and CSF extravasation around the reservoir are signs of an Ommaya reservoir infection.
   c. A chemical meningitis can sometimes occur.
9. About 50% of patients with LM from solid tumors respond to treatment (mostly breast cancer); about 75% with lymphoma or leukemia do. Response in solid tumors is less as available IT agents are more effective for hematologic malignancies.
10. MTX is the most commonly used drug for IT management of solid tumors.
11. Cytarabine for IT use is available encapsulated into multivesicular lipid-based particles. Severe or life-threatening arachnoditis from this treatment occurs in 19% to 30% of patients but its incidence and severity can be reduced by co-administration with dexamethasone. The terminal half-life of cytarabine in CSF can reach up to 82 hours and systemic exposure is minimal.

VII. METASTASIS TO THE SPINAL CORD PARENCHYMA

A. Treatment is palliative.

1. Dexamethasone is the initial treatment and should be followed by RT to the affected area.
2. Because approximately 75% of cases are secondary to lung and breast cancer and lymphoma, some clinical improvement can be expected, especially if the patient is treated before a myelopathy develops.
3. Surgical decompression accomplishes little because the disease is intrinsic to the spinal cord, and resection of the lesion itself is generally not feasible.

VIII. METASTASIS TO THE PERIPHERAL NERVOUS SYSTEM

A. Presentation.

1. Pain, numbness, paresthesiae, or weakness.
2. Must be differentiated from RT plexopathy, which is painless.

B. Treatment.

1. Aggressive pain relief is imperative.
2. Nonnarcotic drugs fail early, and adequate doses of narcotics should be prescribed.
3. If narcotics fail, several anesthetic or neurosurgical procedures are available.
4. RT or chemotherapy is used as appropriate.

IX. NEUROLOGIC COMPLICATIONS OF CHEMOTHERAPY

A. Most cytotoxic drugs can cause neurotoxicity as can some of the biologic agents. Reasons for recognizing iatrogenic toxicity are:

1. Drug toxicity can obscure or mimic the presentation of metastasis, paraneoplastic syndromes, or primary neurologic disease.
2. Neurotoxicity can contribute to morbidity, disability, and death.
3. Neurotoxicity can result from metabolic derangement of therapy or cancer-induced end-organ failure.
4. The offending agent can be identified during treatment with a multiple-drug regimen.

B. Common complications attributable to chemotherapy.

1. **Peripheral neuropathy.** Any chemotherapy can cause neuropathy (see Chapter 46), but most commonly implicated are vinca alkaloids, platinum-based agents, taxanes, etoposide, and suramin.
   a. **Vinca alkaloids.** Length-dependent sensorimotor neuropathy from interference with axonal microtubule assembly is the dose-limiting side effect; it produces mild neuropathy in almost all patients at conventional doses. Autonomic dysfunction (gastroparesis, urinary retention, constipation, and ileus) can manifest early. Sometimes, cranial nerve involvement such as facial sensory loss, facial weakness, or recurrent laryngeal nerve palsy occurs. Reduction in dose or early withdrawal leads to complete recovery.
   b. **Cisplatin.** Neuropathy is the dose-limiting side effect; it can develop even months after the drug is stopped. Large-fiber sensory neuropathy and ototoxicity are common, especially with cumulative doses >400 mg per m^2. Symptoms include hearing loss, paresthesia, proprioceptive loss, ataxia and a Lhermitte's sign (sudden, transient electric-like sensation spreading down the body when flexing the head). Autonomic symptoms (see above) are frequent. Most patients improve spontaneously if the total dose is <500 mg per m^2.
   c. **Oxaliplatin** causes acute and chronic peripheral neuropathy. Acute neurotoxicity can occur during or up to 2 days post-infusion and causes neuropathic symptoms (paresthesias, hypesthesias, and dysesthesiae), beginning in the hands or feet, perioral or in the throat. Acute side effects occur at a dose of about 130 mg per m^2. Patients may develop a sense of dyspnea or dysphagia, may describe unusual sensations in the tongue, jaw spasms, eye pain, and muscle spasms or cramps that are sometimes described as stiffness in hands or feet or inability to release their grip. Cold temperature exacerbates the symptoms so patients should avoid cold drinks, wear gloves when handling refrigerated items, and avoid inhaling cold air. Symptoms usually last only a few days. Oxaliplatin causes prolonged opening of sodium-gated channels on peripheral nerves and leads to hyperexcitability from sequestration of calcium by the oxaliplatin–oxalate metabolite. Lowering the dose or increasing the infusion time may lessen the occurrence of these symptoms. Administering calcium gluconate and magnesium chloride decreases the occurrence of pharyngolaryngeal dysesthesia. More prolonged administration of oxaliplatin (total doses 540 to 850 mg per m^2) causes neuropathic symptoms, changes in proprioception that do not resolve between cycles and Lhermitte's sign. The chronic neuropathy is cumulative, with grade 3 toxicity occurring in 10% after 9 cycles, and in approximately 50% at 12 to 14 cycles (doses of 85 mg per m^2 every 14 days). Urinary retention has been reported but is not common. Symptoms usually last months and resolve or improve to level 2 or 1 toxicity within 12 months. Rare complications include optic neuritis and visual field deficits. Gabapentin can reduce the acute neuropathic toxicity and prevent the chronic form as well.
   d. **Paclitaxel and Docetaxel.** Sensory neuropathy occurs with doses >200 mg per m^2. Painful paresthesia, multimodality sensory loss, ataxia, and mild distal weakness are

common. Loss of the distal muscle stretch reflexes is almost universal. These agents can also cause a myopathy.

e. **Etoposide** is reported to cause axonal neuropathy in up to 10% of cases.

f. **Suramin** causes two distinct patterns of neurotoxicity that may be dose limiting. It causes a length-dependent axonal polyneuropathy or a subacute demyelinating polyradiculoneuropathy resembling Guillain–Barré's syndrome (GBS). Inhibition of nerve growth factor may be the mechanism for neurotoxicity and occurs after peak plasma concentration increases to 0.350 mg per mL. Improvement after plasmapheresis has been reported.

g. **Bortezomib** is a proteosome inhibitor used in the treatment of multiple myeloma. It causes an axonal peripheral neuropathy often worsened in patients with dermatomyositis.

h. Ifosphamide is known to cause encephalopathy and busulfan causes seizures so patients are often placed on AEDs pre-treatment.

2. **CNS toxicity.**

a. The prototype drug is MTX. Route of administration, dosage, and simultaneous use with other neurotoxic therapy (particularly cranial RT) may cause additive or synergistic toxicity.

b. IT MTX may produce aseptic meningitis within a few hours after administration, and transient or permanent myelopathy.

c. Leukoencephalopathy is a delayed effect of either IT or high-dose systemic administration and can occur in up to 45% if combined with cranial RT or other neurotoxic drugs.

d. High-dose MTX can produce an acute, self-limited neurologic syndrome characterized by encephalopathy or, sometimes, a stroke-like syndrome of unknown causation.

3. **Cerebellar toxicity.**

a. The Purkinje cells are very sensitive to chemotherapy.

b. **Cytarabine.**

(1) Cerebellar toxicity occurs in 8% to 50% of patients given high-dose systemic cytarabine (doses 0.48 g per m^2), especially if older than 60 and with renal dysfunction. Symptoms occur within 24 to 48 hours and manifest with nystagmus and mild ataxia followed by a florid encephalopathic and ataxic syndrome. See VI.G.11. for IT toxicity.

(2) Patients may improve within 1 week and recover completely within 2 weeks.

(3) The pathogenesis of this syndrome relates to the minimal amounts of cytidine deaminase in the CNS.

c. **5-Fluorouracil (5-FU).**

(1) Causes abrupt onset of cerebellar dysfunction in as many as 8% of patients. Symptoms develop a few days to months after initiation of treatment and resolve after drug discontinuation. Cerebellar dysfunction is likely with schedules of one or more weekly boluses of >15 mg per kg and is linked to a deficiency of dihydropyrimidine dehydrogenase.

(2) Can cause an encephalopathy with hyperammonemia and lactic acidosis.

(3) Treatment of metastatic colorectal cancer with 5-FU and levamisole can cause a subacute multifocal leukoencephalopathy. MRI often shows supratentorial and infratentorial multifocal enhancing white-matter lesions.

(4) Other side effects include ophthalmoplegia, optic neuropathy, encephalopathy, focal dystonias, and parkinsonism.

(5) Capecitabine is a 5-FU prodrug that can have CNS toxicity, usually more acutely than 5-FU, but which resolves once the drug is stopped; it can cause diffusion restriction on MRI.

4. **Bevacizumab** is a monoclonal antibody against VEGF.

a. In 0.1% it has been associated with posterior reversible encephalopathy syndrome (PRES), which may present with headaches, seizures, lethargy, confusion, blindness, or other visual disturbances. Hypertension may or may not precede the symptoms. MRI shows characteristic findings of PRES.

b. Arterial thromboembolic events such as stroke, transient ischemic attack, and myocardial infarction may also occur.

c. Bleeding can occur—when intracranial or intratumoral, it can be fatal.

X. OTHER COMPLICATIONS

A. Neuropathic pain. Common neuropathic pain syndromes are:

1. **Brachial plexus pain.** Tumor invasion of the brachial plexus from breast carcinoma leads to pain most often referable to a C8-T1 distribution. Pain may precede neurologic findings by months. Management of the underlying tumor relieves pain in approximately 50% of cases. If pain returns, an exhaustive search for tumor recurrence must be undertaken.
2. **Lumbar plexus pain.** The lumbar plexus is commonly involved in extension of pelvic and colon tumors or metastasis from distant tumors (see Chapters 23 and 25).
3. **Base of skull metastasis.** (See III.) Pain in the face may be shock-like, and referable to the orbit or brow area. **Swallow syncope** refers to the occurrence of lightning-like pain upon swallowing followed by syncope. It is often caused by tumors involving the glossopharyngeal nerve (see Chapter 7).
4. **Carcinomatous meningitis.** Tumor seeding along nerve root sleeves may produce polyradicular pain symptoms.
5. **Postsurgical pain.** Five percent to twenty percent of patients undergoing mastectomy have characteristic postmastectomy pain characterized by a burning, tight feeling in the upper inner arm and across the chest. This may lead to a "frozen shoulder." Thoracotomy is also very painful in the immediately postoperative period because the intercostal nerves are subjected to direct trauma during the procedure. Radical neck dissection can lead to poorly defined burning, stabbing pain from injury to the cervical nerves.
6. **Radiation injury** to peripheral nerves and plexus, although usually painless, can have painful sequelae with onset usually delayed for years after exposure. Pain may be the initial presentation of cervical plexus injury, whereas lumbar plexus injury often manifests as weakness. These must be differentiated from tumor recurrence.
7. **Chemotherapy-related pain.** Neuropathy caused by chemotherapeutic agents can be painful.
8. **Treatment.** Opioids are considered the mainstay of treatment. Other agents commonly used include tricyclic antidepressants, including tertiary and secondary amines. AEDs such as carbamazepine, gabapentin, and pregabalin are also used. Corticosteroids have been used in a variety of settings mainly as an adjunct to opioids. Local anesthetics such as capsaicin- and lidocaine-based creams and patches can also be used (see Chapter 50).

B. Encephalopathy.

1. **Seizures.**
   a. Encephalopathic conditions can cause seizures, and seizures can cause encephalopathy.
   b. A postictal state can mimic encephalopathy; in debilitated, elderly patients it can last 1 week or more.
2. If treatable causes are excluded, management is supportive.

C. CNS infection (see Chapters 43 and 44).

1. The most frequent organisms are *Listeria monocytogenes*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*.
2. Next in frequency are gram-negative rods, *Candida albicans*, and varicella zoster virus.
3. Latent mycobacterial infections may become reactivated.
4. **Presentation.**
   a. CNS infections often manifest as fever, changes in mental status, and seizures (see Chapter 43).
   b. Headache and stiff neck can be subtle if patients are unable to mount an adequate inflammatory response.
   c. In leukopenic patients, the CSF may not be purulent, and the infecting organism may not be readily detectable.
   d. Gram staining or a polymerase chain reaction of cytospin sediment may reveal the pathogen before cultures.
5. *LP should be approached with caution* because a patient with increased ICP may herniate, or a patient with underlying thrombocytopenia may develop an epidural or subdural hematoma.
6. **Treatment** consists of antibiotics and support.

7. **Progressive multifocal leukoencephalopathy (PML) (see Chapters 43 and 44)**.
   a. PML is a CNS infection by an opportunistic papovavirus, the JC virus.
   b. Rare cases go into long-term remission but most patients die of this disorder.
   c. PML manifests as changes in mental status, speech and vision deficits, and weakness.
   d. Diagnosis is from biopsy of a focal (nonenhancing) white-matter brain lesion if CSF for JC virus is negative.
   e. Treatment with adenosine arabinoside (Ara-A) or cytarabine is of unproven benefit.
   f. May be seen in patients treated with rituximab.

D. Cerebrovascular (CV) complications.

1. At autopsy, approximately 15% of cancer patients are found to have CV disease.
2. Atherosclerosis remains the leading cause of infarction, but only approximately 15% of infarcts are symptomatic.
3. Patients with cancer may also develop CV disease as a complication of the neoplastic process or its management.
4. Ischemic infarcts, rather than hemorrhages, predominate among patients with carcinoma. Nonbacterial thrombotic endocarditis (NBTE) and disseminated intravascular coagulation are frequent causes of symptomatic cerebral infarction in this population.
5. The most frequent causes of intraparenchymal hemorrhage are coagulopathies and hemorrhage into metastatic lesions from melanoma and germ cell tumors.
6. Mucinous cancers may produce infarction from occlusion of any cerebral artery.
7. A large proportion of patients with symptomatic CV disease and leukemia may experience hemorrhagic infarctions.
8. There is no specific therapy for these complications.
9. Chemotherapy, especially with cisplatin, can cause both acute and late vasculo-occlusive complications.
   a. Acute vascular occlusion may be related to endothelial injury.
   b. Late vascular occlusive abnormalities may be related to vasospasm from underlying hypomagnesemia.
10. **Late effects of RT** include a noninflammatory arteriopathy, causing large- and small-vessel occlusion, a mineralizing microangiopathy, or accelerated atherosclerosis.
11. **Dural venous sinus thrombosis,** particularly of the superior sagittal sinus (SSS), is underdiagnosed.
    a. It is frequently asymptomatic and eventually recanalizes.
    b. It is most frequent in patients with leukemia receiving chemotherapy (especially L-asparaginase), and in patients with underlying coagulopathies or widespread cancer especially with a large amount of skull metastases.
    c. It manifests as headache, seizures, papilledema, focal motor signs, and encephalopathy.
    d. Diagnosis is made by means of contrast-enhanced CT, MRI, MR angiography or venography.
    e. Treatment is supportive, with short-term anticoagulation, if not clinically contraindicated.
12. **Neoplastic angioendotheliosis** or intravascular lymphomatosis, a rare complication of lymphoma, is intravascular occlusion of small blood vessels by malignant mononuclear cells.
    a. When in the CNS, patients have multifocal deficits and encephalopathy with short-term or subacute progression to death.
    b. This disorder is difficult to differentiate from PML, CNS vasculitis, and multiple emboli.
    c. It can respond to treatment.
13. Patients with Waldenström's macroglobulinemia can develop neurologic symptoms from peripheral neuropathy or CNS symptoms from hypervisocity or brain infiltration (Bing-Neel's syndrome).

E. Syncope in patients with head and neck cancer.

1. This manifests in advanced or recurrent disease as syncope accompanied by paroxysmal head and face pain.
2. An abnormally strong carotid sinus reflex mediates the syncopal attacks.
3. A relation between the syncope and sudden death exists and should prompt a search for recurrent carcinoma.
4. Pain is managed with an AED such as gabapentin, pregabalin, or carbamazepine.

5. Syncope is managed with anticholinergic drugs such as propantheline at 15 to 30 mg orally four times a day; ephedrine at 25 mg orally four times a day may be added if there is a vasodepressor component and florinef may be used.

XI. PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes, or remote effects of cancer, are thought to originate from production of an antibody to onconeural antigens shared between the tumor and the CNS. Paraneoplastic neurologic syndromes may involve any part of the CNS or PNS. They must be differentiated from treatment-related toxicity and from metastasis. The antibodies found in these disorders are not thought to be directly pathogenic and should be considered as markers for these disorders. T-cell cytotoxic mechanisms might play an important role in nervous system injury. Any paraneoplastic syndrome may precede diagnosis of the underlying malignancy by up to several years. The best characterized paraneoplastic syndromes are

A. **Paraneoplastic limbic encephalitis** may develop in isolation or in association with disorders of brainstem, cerebellum, or peripheral nerves. The most common associated tumor is SCLC, followed by germ cell tumor, testicular tumors, breast, thymoma, and Hodgkin's lymphoma.

1. **Clinical features.**
   a. Most characteristic is a subacute amnestic syndrome with relative preservation of other cognitive functions. Short-term anterograde and variable retrograde amnesia are present. Memory deficit may be preceded by weeks of depression, personality changes, and emotional lability. Partial complex seizures are common.
   b. Most patients eventually manifest a more generalized multifocal encephalomyelitis with involvement of brainstem, cerebellum, dorsal root ganglia, spinal cord, and autonomic nervous system.
   c. The course is variable and unpredictable. Most patients appear to stabilize at a level of severe disability; a few patients become obtunded and comatose.
2. **Diagnosis.**
   a. Anti-Hu antibodies are present in 50% of patients with SCLC and symptoms suggestive of limbic encephalitis. Prognosis is better among patients without anti-Hu antibodies.
   b. Anti-Ta, anti-Ma1, and anti-Ma2 antibodies have been identified in the CSF and serum of patients with this syndrome.
   c. "Atypical antibodies" including anti-CV2 associated with thymoma and antibodies that stain hippocampal neurons in patients with colon cancer have also been reported.
   d. T2-weighted or FLAIR MRI may show abnormalities in the mesial temporal lobes (Fig. 53.2). CSF may demonstrate inflammatory changes, including increased protein content, moderate pleocytosis, presence of oligoclonal bands, and an increased level of immunoglobulin G (IgG).

B. **Anti-NMDA receptor (NMDAR) encephalitis** is a severe syndrome with psychiatric symptoms (such as agitation, paranoia, hallucinations, and irritability) and seizures associated with antibodies to the NR1 subunit of the NMDAR in women with ovarian teratomas. Outcome is favorable following removal of the teratoma.

C. **Paraneoplastic cerebellar degeneration (PCD)** may be profoundly disabling. PCD is more common among women and is often associated with adenocarcinoma of the ovary, uterus or adnexa, carcinoma of the breast, SCLC, and less commonly with Hodgkin's lymphoma. In the setting of gynecologic malignancies, PCD usually occurs as an isolated syndrome. In the setting of SCLC, PCD often occurs as a part of more diffuse CNS involvement.

1. **Clinical features.**
   a. The most common initial symptom is loss of coordination. Vertigo, nausea, and vomiting are common. Progression is usually subacute. Most patients display trunk and gait ataxia and dysarthric speech. Head titubation may be present.
   b. **Examination** usually demonstrates ocular dysmotility, including nystagmus, limb dysmetria, and occasionally, opsoclonus. Patients are often left with a severe neurologic deficit without much improvement.

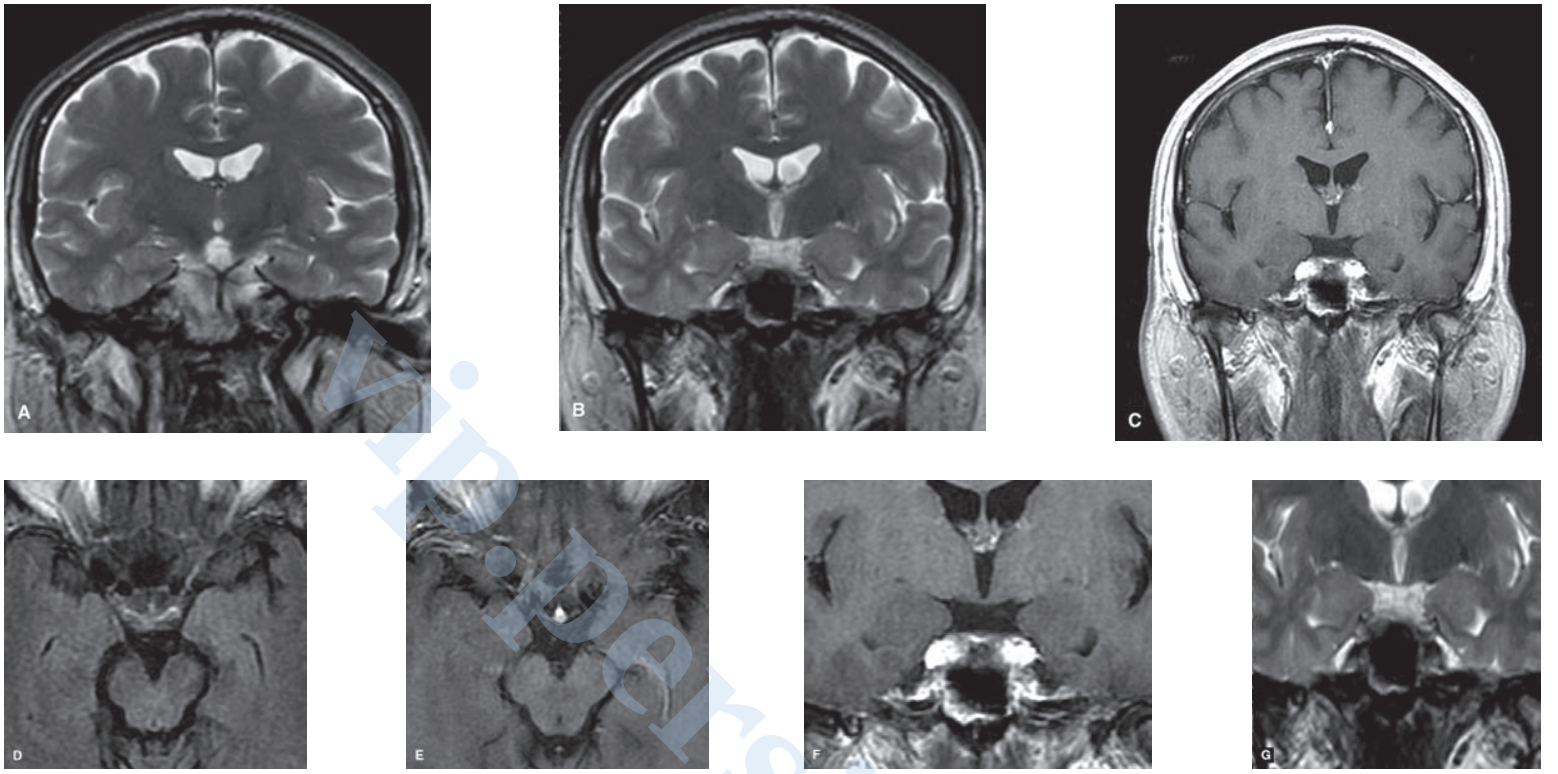

FIGURE 53.2 MRI of the brain in a patient with paraneoplastic limbic encephalitis associated with lung carcinoma demonstrates hyperintense signal in the medial temporal lobes. Note on T2 images increased signal and thickness in the mesial temporal lobe structures, and on post-contrast T1 images the presence of edema and the lack of significant enhancement. (Courtesy of José Biller, MD.)

2. **Diagnosis.**
   a. Three major and several minor patterns of antineuronal antibody patterns have been associated with PCD. Only one of these, the anti-Yo antibody (type 1 antiparietal cell antibody) is strictly associated with PCD and is present exclusively in women with gynecologic malignancies or breast carcinoma. The other two, the anti-Hu (type 2, antineuronal nuclear antibody type 1) and the anti-Ri (type 2b, antineuronal nuclear antibody type 2) are associated with more complex disorders that may initially be diagnosed as PCD.
   b. The anti-Hu pattern is associated with SCLC, and the anti-Ri with breast carcinoma. Other antibodies include anti-Tr autoantibodies described in patients with Hodgkin's disease, and the anti-CV2 in patients with lung cancer. Most patients with PCD in association with Hodgkin's disease, non-SCLC, or gastrointestinal carcinoma do not have any demonstrable antineuronal antibodies.
3. **Management.** Treatment is unsatisfactory, with best results among patients with no underlying gynecologic malignant tumors. Plasmapheresis or administration of IV immunoglobulin (IVIg) is beneficial in fewer than 10% of patients.

D. **Opsoclonus–myoclonus (OM)** is characterized by random, chaotic ocular movements. It is reported to occur with a variety of tumors and occurs in approximately 2% to 3% of children with neuroblastoma. Paraneoplastic OM usually appears as a part of a constellation of symptoms that include some combination of ataxia, myoclonus, and alteration in mental status.

1. **Clinical features.** Eye movements are conjugate, high amplitude, and in all directions of gaze. They are almost continuous and persist during eye opening. Unlike other paraneoplastic disorders, OM may go into spontaneous remission and be relieved with immunosuppressive therapy or tumor treatment. No clinical features differentiate paraneoplastic from non-paraneoplastic OM.
2. **Diagnosis.** Remains clinical, but patients with opsoclonus and ataxia associated with breast cancer may have anti-Ri antibodies. Patients with SCLC and opsoclonus usually have no detectable antineuronal antibodies. MRI of the brain is usually normal. Children with opsoclonus need a complete evaluation for neuroblastoma, including nuclear imaging with metaiodobenzylguanidine.
3. **Management.** Corticotropin or corticosteroids produce rapid and dramatic neurologic improvement in at least two-thirds of children independently of tumor status. In a number of adult patients with or without antineuronal antibodies, improvement has followed treatment with corticosteroids.

E. **Myelopathy** can occur with multiple-system neurologic involvement, as in paraneoplastic encephalomyelitis, in which case cord involvement is patchy. Necrotizing myelopathy, a distinct clinical entity, also occurs independently. Necrotizing myelopathy can occur in association with a variety of carcinomas and lymphoid tumors.

1. **Clinical features of necrotizing myelopathy.**
   a. Onset is usually subacute with bilateral symptoms involving motor, sensory, and sphincter dysfunction and little or no pain. Examination shows findings consistent with transverse spinal cord dysfunction. Most patients have rapid deterioration with progressively ascending paralysis. Death may result from respiratory failure.
   b. **Differential diagnosis** in a cancer patient includes intramedullary spinal metastasis, and spinal cord injury caused by RT or by IT chemotherapy.
2. **Diagnosis.** Spinal MRI may be normal or show intramedullary involvement. Although no antineuronal antibodies have been associated specifically with necrotizing myelopathy, in the absence of other causes it is felt to be paraneoplastic.
3. **Management.** There is anecdotal evidence of improvement with corticosteroids.

F. **Motor neuron disease.** Lower motor neuron signs are a predominant manifestation in about 25% of cases of multifocal paraneoplastic encephalomyelitis; most patients have SCLC. However, it is unclear how often pure motor neuron disease is paraneoplastic. As yet, there is no convincing evidence that nonhematogenous neoplasms occur in patients with amyotrophic lateral sclerosis any more frequently than would be expected in an age-matched control population. The prevalence of plasma cell dyscrasias among patients with motor neuron disease is higher than among controls; most

have a monoclonal gammopathy of undetermined significance. Lymphoma has also been described in these patients.

1. **Clinical features.** Patchy weakness, fasciculations, and atrophy are usual manifestations. Patients may also have alteration in mental status, cerebellar ataxia, and brainstem findings.
2. **Diagnosis.** Anti-Hu antibodies may or may not be present.
3. **Management.** Improvement may follow plasma exchange and administration of corticosteroids and alkylating agents such as melphalan.

G. Stiff person syndrome. Muscle stiffness or rigidity may occur in the setting of several paraneoplastic disorders and reflect either CNS or PNS dysfunction. A syndrome resembling stiff person syndrome has been associated with several neoplasms; breast and SCLC most commonly, but also Hodgkin's lymphoma, and carcinoma of the colon.

1. **Clinical features.** Patients have increasing aching and rigidity of axial and proximal limb muscles with sparing of the face. Severe painful spasms may occur spontaneously, or are precipitated by movements or sensory stimuli. Some patients display a fixed posture or opisthotonus in later stages of the disease.
2. **Diagnosis.** EMG shows continuous firing of motor units during the spasms. Most patients have serum and CSF antibodies against amphiphysin, a synaptic vesicle-associated protein but they are not specific for this syndrome and have also been found among patients with limbic encephalitis, PCD, or sensory neuronopathy. In contrast, antibodies to glutamic acid decarboxylase are found in stiff man syndrome of non-neoplastic origin.
3. **Management.** Some patients improve after tumor treatment. Benzodiazepines, baclofen, tizanidine, or prednisone might provide symptomatic relief.

H. Retinal degeneration (carcinoma-associated retinopathy) is a heterogenous disorder with varying tumor associations and different pathophysiologic mechanisms. More than 90% of patients have SCLC. Melanoma also is frequently associated.

1. **Clinical features.** Patients complain of bilateral visual blurring or dimming. Night blindness is a common complaint, especially among patients with melanoma. Positive visual symptoms such as sparkles and shimmering lights may be present. Examination may show an afferent pupillary defect and mild to moderate arteriolar narrowing. Otherwise, the examination is often unremarkable.
2. **Diagnosis.** The most common encountered antibody is the polyclonal IgG anti-CAR antibody. These antibodies react with recoverin, a calcium-binding protein. Some patients may also have antibodies against unidentified retinal proteins. However, many patients with cancer-associated retinopathy have no detectable antineuronal antibody.
3. **Management.** Most patients have mild to moderate improvement with oral prednisone. Management of the tumor appears to have no significant effect on this condition.

I. Neuronopathy.

1. **Subacute sensory neuronopathy.** More than 90% of patients have SCLC. Other neoplasms include carcinoma of the breast, prostate, colon, and lymphoma.
   a. **Clinical features.** Development is subacute, and symptoms may begin in the face, trunk, or abdomen, and may be unilateral. Earliest symptoms are patchy numbness and paresthesia that may spread. Examination usually demonstrates involvement of all sensory modalities with loss of muscle stretch reflexes, flexor plantar responses, and preserved muscle strength if subacute sensory neuronopathy is the isolated or predominant paraneoplastic syndrome. Pseudoathetoid movements of the limbs may be present. Most patients stabilize at a severe level of disability.
   b. **Diagnosis.**
      (1) Most patients have anti-Hu antibodies in serum and CSF, usually in association with SCLC.
      (2) Nerve conduction studies show reduced or absent sensory nerve action potentials and normal or borderline motor nerve conduction velocities. Some patients have features of both axonal and demyelinating neuropathy (see Chapter 33).
      (3) CSF examination usually shows pleocytosis with mononuclear predominance, increased protein level, intrathecal IgG synthesis, and presence of oligoclonal bands.

(4) In patients with known cancer, neuronopathy is often due to the toxic effects of chemotherapy, metastasis, and nutritional deficits. Common drugs implicated are cisplatin, taxanes, and vinca alkaloids.

c. **Management.** Corticosteroids, plasma exchange, and administration of IVIg may be effective.

2. **Demyelinating neuropathy associated with neoplasms.** There are reports of acute, predominantly motor polyradiculoneuropathy occurring in the setting of a number of neoplasms, especially lymphoma. CSF and electrodiagnostic findings resemble those of GBS. Several cases of sensorimotor neuropathy fulfilling criteria for chronic inflammatory demyelinating polyneuropathy have been documented among patients with lymphoma.
3. **Lambert–Eaton myasthenic syndrome (LEMS).** In approximately 50% of cases, the LEMS is associated with a carcinoma, most commonly SCLC. An antibody for the P/Q type voltage-gated calcium channel is found in most patients with LEMS. The LEMS is discussed in further detail in Chapter 48.

J. Some patients have onconeural antibodies in the absence of a malignancy and may remain as such but need surveillance to be sure no malignancy develops; PET scans are the modality of choice.

Recommended Readings

Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004;363:1665–1672.

Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295:2483–2491.

Cestari DM, Weine DM, Panageas KS, et al. Stroke in patients with cancer, incidence and etiology. *Neurology*. 2004;62:2025–2030.

Deangeles LM, Posner JB, eds. *Neurologic Complications of Cancer*. 2nd ed. New York, NY: Oxford University Press; 2009.

Greenberg HS, Deck MDF, Vikram B, et al. Metastasis to the base of the skull: clinical findings in 43 patients. *Neurology*. 1981;1:530–537.

Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. *J Clin Oncol*. 2005;23:6207–6219.

Loblaw DA, Perry J, Chambers A, et al. Systematic review of the diagnosis and management of malignant extradural spinal cord compression: the cancer care Ontario practice guidelines initiative's neuro-oncology disease site group. *J Clin Oncol*. 2005;23:2028–2037.

Patchell R, Tibbs P, Regine W, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet*. 2004;366:643–648.

Pruss H, Dalmau J, Harnms L, et al. Retrospective analysis of NMDA antibodies in encephalitis of unknown origin. *Neurology*. 2010;75:1735–1739.

Rogers LR. Cerebrovascular complications in cancer patients. *Neurol Clin*. 2003;21:167–192.

Rosenfeld MR, Dalmau J. Update on paraneoplastic and autoimmune disorders of the central nervous system. *Semin Neurol*. 2010;30:320–331.

Sirven JI, Wingerchuk DM, Drazkowski JF, et al. Seizure prophylaxis in patients with brain tumors: a meta-analysis. *Mayo Clin Proc*. 2004;79:1489–1494.

Titulaer MJ, Soffieti R, Dalmayu J, et al. Screening for tumors in paraneoplastic syndromes: report of an EFNS task force. *Eur J Neurol*. 2011;18:19-e3.

Vecht CJ, van Breemen M. Optimizing therapy of seizures in patients with brain tumors. *Neurology*. 2006;67:S10–S13.

Vogelbaum MA, Suh JH. Resectable brain metastases. *J Clin Oncol*. 2006;24:1289–1294.

CHAPTER

54 Neurotoxicology

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Neurotoxins are compounds that are toxic, or potentially toxic, to the central and/or peripheral nervous system. Capable of mimicking neurologic disorders, neurotoxins can be classified into one of three categories: (1) **drugs** (prescription and illicit), (2) **chemicals** (industrial, household, and abused agents), and (3) **environmental** (biologic agents and naturally occurring chemicals).

Establishing causation is paramount to the correct diagnosis and the treatment for any patient with a suspected neurotoxic syndrome. The steps involved in determining if a neurotoxin is the causative agent are those established by Sir Austin Bradford Hill in differentiating association from causation in epidemiologic studies.

1. **Exposure.** Did an exposure occur? Requires quantifying the level of a toxin in biologic specimens (blood, urine, and hair) or in the environment (air and water). In some cases, historical features alone may be adequate.
2. **Temporality.** Did symptoms begin concurrent with or after the exposure? A few toxins have long latent periods before symptoms develop but most cause symptoms that begin shortly after exposure.
3. **Dose–response.** Do persons with higher doses and longer exposures have more severe symptoms?
4. **Similarity to reported cases.** Are the symptoms similar to those previously reported?
5. **Improvement as exposure is eliminated.** Do symptoms improve when the toxin exposure is eliminated or reduced? Most toxin-induced symptoms improve after cessation of exposure; although a period of worsening symptoms, or even chronic symptoms, can occur after exposure to a few toxins.
6. **Existence of animal model.** Do animal studies establish biologic feasibility? Animal studies can be helpful to predict toxicity in the absence of human studies; although some toxins do not have animal models and some toxins affect animals differently than humans.
7. **Other causes eliminated.** Are nontoxicologic causes excluded?

This overview is intended as a quick reference of those toxins clinicians are most likely to encounter. For more detailed work on the topic, see the recommended readings.

I. PERIPHERAL NERVOUS SYSTEM

A. Peripheral neuropathy. Toxic peripheral neuropathies typically present as acute or subacute, symmetric axonopathies, affecting the distal axons of the lower extremities.

1. **Heavy metals.**
   a. **Arsenic.**
      (1) **Sources.** Ground and well water, seafood (organic arsenic, nontoxic), paints, fungicides, insecticides, pesticides, herbicides, wood preservatives, cotton desiccants, and homicidal agents.
      (2) **Route of exposure.** Ingestion is the most common, but absorption through skin and inhalation can occur.
      (3) **Acute toxicity.**
         (a) **Systemic signs.** Gastrointestinal (GI; nausea, vomiting, abdominal pain, and bloody diarrhea) symptoms occur within 24 hours of exposure; if severe, can be followed by hypovolemic shock, pancytopenia, and ventricular arrhythmias.
         (b) **Neurologic manifestations.** Within 2 weeks, patients may develop a distal symmetric peripheral neuropathy presenting with burning and numbness in the feet. May present as ascending weakness similar to Guillain–Barré's syndrome. Encephalopathy can develop in severe poisoning.

(4) **Chronic toxicity.**
   (a) **Systemic signs.** Hypertension, peripheral vascular disease, renal failure, hepatitis, and keratoses of the palms and soles; associated with cancers of the skin, lung, liver, bladder, kidney, and colon.
   (b) **Neurologic manifestations.** Peripheral neuropathy, stocking-glove distribution, and sensory > motor.

(5) **Physical examination findings.** Hyperpigmentation and keratosis develop on the palms and soles. Mees lines (transverse semilunar white bands across the nails) may be present in a minority of cases and may take as long as 40 days to develop.

(6) **Mechanism of toxicity.** Trivalent arsenite binds sulfhydryl groups on critical enzymes inhibiting the Krebs cycle and oxidative phosphorylation. Pentavalent arsenate uncouples oxidative phosphorylation.

(7) **Diagnosis.**
   (a) **Laboratory.** The **24-hour urine** arsenic concentration is the gold reference standard for confirming recent exposures (<30 days): normal results <50 µg per L or <100 µg per 24 hours. False-positive results are common after seafood ingestion (from nontoxic organic arsenic) and necessitate repeating after abstaining from seafood. **Blood** testing (normal result <7 µg per dl) is less reliable owing to short half-life of arsenic. **Hair** testing (normal <1 mg per kg) may be useful for chronic or remote exposures.
   (b) **Radiographs.** May show radiopacities in the GI tract.
   (c) **Nerve conduction studies (NCS).** Severe acute exposure may cause conduction slowing characteristic of proximal demyelination (similar to acute inflammatory demyelinating polyradiculopathy), and distal, motor, and sensory axonopathy. In less severe, or chronic, exposures patients develop a distal, sensory greater than motor axonopathy.
   (d) **ECG** can show a prolonged QT interval with risk for torsades de pointes.

(8) **Treatment.**
   (a) Removal of exposure.
   (b) If material is retained in the GI tract, consider either whole-bowel irrigation or use of cathartics.
   (c) If clinical presentation is highly suggestive, then begin chelation therapy before laboratory confirmation.
      i. **Dimercaptosuccinic acid (DMSA)** is useful in the treatment of subacutely or chronically poisoned patients (10 mg per kg by mouth three times a day for 5 days then twice a day until the urinary arsenic level is <50 µg per L per 24 hours). Complications include transient increases in liver function tests.
      ii. **British anti-Lewisite (BAL)** is useful in severe exposures when oral therapy cannot be given or the patient has an ileus (3 to 5 mg per kg intramuscularly [IM] every 4 to 6 hours until urinary arsenic level is <50 µg per kg per 24 hours). Complications include pain over the injection site, hypertension, febrile reactions, and agitation.
      iii. **Dimercaptoproprane-1-sulfonate** is not approved in the United States but used in other countries (loading dose of 1,200 to 2,400 mg per day in equal divided doses [100 to 200 mg 12 times daily] followed by maintenance of 100 mg orally two to four times a day).
   (d) **RBC and plasma exchange** may be useful to remove components of RBC lysis and to further reduce arsenic levels in cases of intravascular hemolysis from arsine gas poisoning.

b. **Lead.**

(1) **Sources.** Lead-based paint (houses painted before 1978), soil, ceramic glaze, gun ranges, battery manufacturing, retained foreign bodies, and ethnic folk remedies.

(2) **Route of exposure.** Ingestion or inhalation.

(3) **Systemic signs.** Abdominal pain, anorexia, constipation, anemia, nephropathy (Fanconi's syndrome), hypertension, and rarely gout.

(4) **Neurologic manifestations.**

(a) **CNS** signs are more common in children: encephalopathy, coma, visual perceptual defects, seizures, and signs of increased intracranial pressure (bulging fontanel or papilledema).
(b) **PNS** signs are more common in adults: peripheral neuropathy manifesting as a motor axonopathy (arms > legs and extensors > flexors [causes foot or wrist drop]). It can be symmetric or asymmetric.

(5) **Physical examination findings.** Bluish black lines around gums (Burton's lines) are rarely noted.
(6) **Mechanism of toxicity.** In children, lead affects many neurotransmitters by increasing the release of dopamine, acetylcholine, and γ-amino butyric acid, and by blocking *N*-methyl-D-aspartate glutamate receptors. Disruption of intercellular junctions interferes with the blood–brain barrier causing capillary leakage and increasing pressure. In adults, lead causes Schwann cell destruction followed by demyelination and axonal destruction.
(7) **Diagnosis.**
(a) **Laboratory.** The gold standard for testing is **blood lead** levels. Normal result is <10 μg per dl. In **children** levels >10 μg per dl necessitate investigation and environmental lead reduction. Levels >45 μg per dl necessitate chelation. In **adults,** levels >40 μg per dl necessitate removal from work site. Levels >70 μg per dl necessitate chelation. CBC may show microcytic anemia with basophilic stippling.
(b) **Radiographs** may show lead lines (increased metaphyseal densities) in growth plates and retained radiopaque material in GI tract.
(c) **NCS** may show normal or decreased conduction velocity.
(8) **Treatment.**
(a) Remove from exposure.
(b) If material is retained in GI tract, consider either whole bowel irrigation or cathartics.
(c) **Chelation therapy.**
i. **DMSA** may be used as the sole agent if patients are able to take oral medications (10 mg per kg by mouth three times a day for 5 days and then three times a day for 14 days, after 1-week remeasure the lead level). Start for levels >45 μg per dl in children, or for symptomatic adults with levels >70 μg per dl. Continue until levels are <25 μg per dl in children or <30 μg per dl in adults.
ii. **BAL** (3 to 5 mg per kg IM four times a day if unable to take orals).
iii. **Ethylenediaminetetraacetic acid** (35 to 50 mg per kg every day by continuous intravenous [IV] infusion in combination with BAL). Start 4 hours after initiation of BAL.

c. **Thallium.**
(1) **Sources.** Homicidal agent, rodenticides (no longer in United States), and manufacturing of optic lenses and semiconductors.
(2) **Route of exposure.** Ingestion and dermal.
(3) **Systemic signs.** Constipation, myalgias and arthralgias, alopecia beginning approximately within 2 weeks of exposure.
(4) **Neurologic manifestations.** Within 1 week of exposure, patients develop a rapidly progressive ascending, predominantly sensory, peripheral neuropathy (symptoms are dysesthesias and paresthesias of the feet, and less commonly the hands). Can see encephalopathy, insomnia, and cranial neuropathies.
(5) **Physical examination findings.** Blackened hair roots (under low-power light microscopic) and Mees' lines on fingernails (rarely).
(6) **Mechanism of toxicity.** Interferes with K^+-dependent processes resulting in a decrease in catabolism of carbohydrates and impaired ATP generation through oxidative phosphorylation, inhibits sulfhydryl-containing enzymes.
(7) **Diagnosis.** Twenty-four hour urine thallium concentration (normal <10 μg per specimen), hair thallium concentration (normal <20 ng per g), examination of darkened hair roots under light microscopy, and NCS show sensorimotor axonopathies with severity of abnormalities correlating with the severity of symptoms.

(8) **Treatment. Prussian blue** (3 g orally three times a day). If Prussian blue cannot be obtained, multidose activated charcoal should be given until available.

d. **Mercury.**

(1) **Sources.** There are three forms that differ in characteristic and toxicity.

(a) **Elemental mercury.** Used in thermometers, barometers, thermostats, electronics, batteries, and dental amalgams.

(b) **Inorganic mercury salts.** Found naturally as mercury (II) sulfide, mercuric chloride, mercuric oxide, mercuric sulfide, mercurous chloride, mercuric iodide, ammoniated mercury, and phenylmercuric salts. These compounds have been used in cosmetics and skin treatments. Most exposures come from old skin products and exposure to germicides, pesticides, and antiseptics.

(c) **Organic mercury.** Used as preservatives and antiseptics, and previously common for industrial and medicinal purposes in the early 20th century. Ethyl mercury (thimerosal) was used in multidose vaccine vials, although it has been recently removed. Methyl mercury exposure occurs through the consumption of predatory fish.

(2) **Route of exposure. Elemental mercury** exposure occurs by inhalation of the vapor, ingestion of the liquid, or cutaneous exposure. Ingestion and cutaneous exposure are of little clinical consequence as mercury is poorly absorbed via these routes. Ingestion of **inorganic mercury salts** results in the greatest absorption, but it may also be inhaled and dermally absorbed. **Organic mercury** exposure occurs primarily by ingestion and dermal absorption.

(3) **Systemic signs.**

(a) **Elemental mercury. Acute toxicity** presents within hours of a large inhalational exposure with GI upset, chills, weakness, cough, and dyspnea. Patients may progress to adult respiratory distress syndrome and renal failure. **Chronic toxicity** develops over weeks to months, depending on the level of exposure and presents with constipation, abdominal pain, poor appetite, dry mouth, headache, and muscle pains.

(b) **Inorganic mercury salts** are corrosive to the GI mucosa causing oral pain, burning, nausea, vomiting, diarrhea, hematemesis, bloody stools, or abdominal discomfort with ingestions. Patients may develop acute tubular necrosis within 2 weeks exposure and membranous glomerulonephritis and nephrotic syndrome with chronic exposures.

(c) **Organic mercury.** Patients may develop renal failure.

(4) **Neurologic manifestations.**

(a) **Elemental mercury. Chronic** exposure can produce proximal weakness involving the pelvic and pectoral girdle. Patients can develop erethism (memory loss, drowsiness, lethargy, depression, and irritability). Patients can also suffer from incoordination, fine motor tremor of the hands, and a sensorimotor neuropathy without conduction slowing.

(b) **Inorganic mercury salts.** Patients can develop erethism as above.

(c) **Organic mercury.**

i. **PNS.** Paresthesias of mouth and extremities occur as result of a predominantly sensory neuropathy.

ii. **CNS.** Damage occurs to gray matter of cerebral and cerebellar cortex, mainly affecting the temporal and occipital lobes. Patients present with concentric constriction of bilateral visual fields, ataxia, incoordination, tremor, dysarthria, and auditory impairment. In utero exposure may cause a cerebral palsy-like condition known as Minamata disease.

(5) **Physical examination findings.**

(a) **Elemental mercury.** Oral findings include reddened, swollen gums, mucosal ulcerations, and tooth loss. Patients may display characteristics of acrodynia (sweating, hypertension, tachycardia, weakness, poor muscle tone, and an erythematous desquamating rash to the palms and soles). Symptoms associated with acrodynia may mimic the presentation of pheochromocytoma (mercury also may elevate catecholamine levels).

(b) **Inorganic mercury salts.** Prolonged use can cause skin changes including hyperpigmentation most pronounced in skin folds of face and neck, swelling, and a vesicular or scaling rash. Patients can develop symptoms associated with acrodynia as described above.

(c) **Organic mercury.** Mainly display abnormal neurologic exams as described above in **I.A.1.d.(4).(c).**

(6) **Mechanism of toxicity.** All three forms combine with sulfhydryl groups on cell membranes and interfere with cellular processes.

(7) **Diagnosis.**

(a) **Elemental mercury.** Clinical presentation, history of exposure, and elevated body burden of mercury. Because of a short half-life, blood levels have limited usefulness (concentrations are typically <10 μg per L). Twenty-four-hour urine levels are normally <50 μg of mercury.

(b) **Inorganic mercury salts.** Twenty-four-hour urine levels are the gold standard.

(c) **Organic mercury.** Best identified in blood or hair as 90% of methylmercury is bound to hemoglobin within the RBCs. Urinary mercury levels are unreliable because methylmercury is eliminated in bile. Normal whole blood values are <0.006 mg per L. Diets rich in fish can increase levels to 0.200 mg per L or higher.

(8) **Treatment.**

(a) **Elemental mercury.** Remove the patient from the source. As there is minimal toxicity from ingestion, there is no role for GI decontamination. The usefulness of chelation therapy remains unclear. Suggested agents include **DMSA, dimercaprol,** and **D-penicillamine** (**doses I.A.1.a.(8).(c).**).

(b) **Inorganic mercury salts.** Volume resuscitation and prompt chelation are critical to prevent renal injury. BAL is effective within 4 hours of ingestion, but DMSA may be substituted if oral intake is tolerated. Hemodialysis is indicated in renal failure for the elimination of dimercaprol–Hg complexes. See **I.A.1.a.(8).(c).** for doses.

(c) **Organic mercury.** Remove from the source. Chelation may be attempted although studies have not demonstrated appreciable improvement. BAL is not recommended because of increased CNS concentrations of mercury post treatment.

e. **Other metals.**

(1) **Cisplatin.** Used in chemotherapy, toxicity manifests as distal symmetric paresthesia that may not occur for months after treatment. NCS show sensory neuronopathy.

(2) **Gold salts.** Used in rheumatoid arthritis, rarely associated with seizures and encephalopathy. Toxicity manifests as distal symmetric sensorimotor polyneuropathy.

(3) **Zinc.** Sources include denture creams and vitamin supplements. Zinc toxicity results in copper deficiency by inhibiting dietary copper absorption. Copper deficiency is associated with anemia, neutropenia, and myeloneuropathy. Diagnosis is made by history and a CBC combined with serum and 24-hour urine copper and zinc levels. Treatment is removal of the zinc-containing product and copper supplementation.

2. Solvents.

a. ***N*-hexane, methyl-*n*-butyl ketone, 2,5-hexandione.**

(1) **Sources.** Exist in industrial and household glues, varnish, cement, and ink.

(2) **Route of exposure.** Inhalational and abused (huffing or bagging).

(3) **Systemic signs.** Anorexia, weight loss, and renal tubular acidosis (mixtures containing toluene).

(4) **Neurologic manifestations.** Distal weakness, paresthesias, sensory loss, and areflexia. Progression of neuropathy may occur for weeks after exposure ends (coasting). NCS show motor > sensory polyneuropathy with reduced sensory and motor amplitudes and prolonged motor conduction velocity.

(5) **Physical examination findings.** Solvent odor on breath and absent Achilles' reflexes.

(6) **Mechanism of toxicity.** Impairs neurofilamentous transport.
(7) **Diagnosis.**
(a) Clinical history and physical examination findings.
(b) Sural nerve biopsy (axonal degeneration, demyelination, and paranodal axonal swelling with neurofilament accumulation).
(c) Electromyography (denervation and decreased recruitment).
(8) **Treatment.** Removal from the source results in improvement, although symptoms may progress for a time after exposure (coasting).

b. **Other solvents.**
(1) **Acrylamide.** Sensorimotor neuropathy.
(2) **Carbon disulfide.** Distal axonal neuropathy with axonal swellings, extrapyramidal signs, and psychosis.
(3) **Ethyl alcohol (chronic).** Sensorimotor neuropathy effecting distal lower extremities first.
(4) **Ethylene oxide.** Distal axonopathy.
(5) **Methyl-ethyl-ketone.** Nontoxic alone, but synergistically promotes peripheral neuropathy from other solvents.
(6) **Methyl bromide.** Both peripheral and pyramidal effects.
(7) **Styrene.** Sensorimotor, demyelinating neuropathy.
(8) **Trichloroethylene.** Cranial mononeuropathies.

3. **Organophosphates or carbamates.**
a. **Sources.** Chemical warfare agents and pesticides.
b. **Route of exposure.** Ingestion, inhalation, and absorption through skin.
c. **Systemic signs.** Cholinergic excess secondary to stimulation of muscarinic receptors resulting in vomiting, diarrhea, lacrimation, salivation, diaphoresis, bronchospasm, bronchorrhea, miosis, bradycardia, or tachycardia (SLUDGE syndrome).
d. **Neurologic manifestations.**
(1) **CNS.** Decreased mental status and seizures.
(2) **PNS.**
(a) **Acute.** Excess acetylcholine causes depolarizing paralysis: fasciculations and cramping followed by flaccid paralysis.
(b) **Intermediate syndrome.** Proximal muscle weakness, including respiratory symptoms, beginning 1 to 4 days after cholinergic phase.
(c) **Organophosphate-induced delayed neurotoxicity.** Occurs 1 to 4 weeks after organophosphate poisoning and manifests as symmetric, distal, predominantly motor polyneuropathy. NCV studies reveal denervation of affected muscles along with reduced amplitude and prolonged conduction velocity.
e. **Physical examination findings:** Miosis, weakness, and signs of cholinergic excess (acute exposure).
f. **Mechanism of toxicity:** Acetylcholine excess.
g. **Diagnosis.**
(1) History and physical examination findings.
(2) **Plasma cholinesterase** is less specific but has a rapid turnaround time (decrease in level by 50% of baseline or serial increasing levels after poisoning indicates exposure).
(3) **RBC cholinesterase** is more specific but has a long turnaround time (decrease of 25% of baseline level indicates exposure).
h. **Treatment.**
(1) Remove from exposure and decontaminate the skin with soap and water.
(2) Respiratory and cardiovascular support.
(3) **Atropine** initial dose of 2 mg IV and then double dose every 5 to 10 minutes until drying of respiratory secretions.
(4) **Pralidoxime** initial dose of 1.5 g IV over 30 minutes and then infusion of 500 mg per hour until resolution of muscle weakness.
(5) **Diazepam** 10 mg or **lorazepam** 2 mg IV for seizures with repetition of dosage as needed.

4. **Gases.**
   a. **Nitrous oxide.**
      (1) **Sources.** Anesthesic agent.
      (2) **Route of exposure.** Inhalation.
      (3) **Systemic signs.** Signs similar to vitamin B_{12} (cobalamin) deficiency including fatigue, depression, psychosis, and glossitis.
      (4) **Neurologic manifestations** include sensorimotor **peripheral polyneuropathy** may result, in addition to **myelopathy** affecting the posterior and anterolateral columns of the cervicothoracic spinal cord. **Optic neuropathy** and **cognitive impairment** may also occur.
      (5) **Physical examination findings.** Megaloblastic anemia, ataxia, sensory loss, weakness, and Lhermitte's sign.
      (6) **Mechanism of toxicity.** Nitrous oxide disrupts methionine synthetase by oxidizing cobalamin (I) to cobalamin(II).
      (7) **Diagnosis.** Patients may have a normal cobalamin level. Elevated serum homocysteine and methylmalonic acid are useful for confirming the diagnosis (cobalamin is involved in their metabolism). MRI of spinal cord may show increased signal intensity in the posterior and lateral columns on T2-weighted images. NCS show mainly sensorimotor axonopathy.
      (8) **Treatment.** Replace vitamin B_{12}: **cyanocobalamin** 1,000 to 2,000 mcg by mouth (P.O.) daily for 1 to 2 weeks followed by 100 mcg P.O. daily, or 1,000 mcg IM daily for 5 days, then 1,000 mcg IM weekly for 4 weeks then, 1,000 mcg IM every 1 to 3 months, or 1,500 mcg intranasally weekly for 3 to 4 weeks, and then 500 mcg intranasally weekly. Patients should slowly improve.
   b. **Ethylene oxide.** Chronic workplace exposure in industry or through the sterilization of hospital supplies can result in symmetric distal sensorimotor polyneuropathy.
5. **Pharmaceuticals.**
   a. **Dapsone.** Chronic use in dermatologic and rheumatologic disorders may result in a motor neuropathy characterized by weakness and atrophy affecting the upper extremities more than the lower. NCS show motor axonopathy. It may also cause anterior ischemic optic neuropathy or optic atrophy.
   b. **Pyridoxine.** Sensory neuropathy can occur from either large acute doses or excessive long-term use. Permanent sensory neuropathy has been reported after massive doses (>50 g) over a short time. Recovery may occur after removal of the drug.
   c. **Other pharmaceuticals** associated with peripheral neuropathy include amiodarone, colchicine, dideoxycytidine, hydralazine, isoniazid, metronidazole, nitrofurantoin, and thalidomide.

B. Toxins affecting ion channels.

1. **Ciguatera poisoning.**
   a. **Sources.** Ingestion of reef fish (barracuda, sea bass, parrot fish, red snapper, grouper, amber jack, king fish, and sturgeon).
   b. **Systemic signs.** Symptoms usually begin within 2 to 6 hours of ingestion and may include abdominal pain, vomiting and diarrhea, dysuria, and pruritus. Cardiovascular symptoms include hypotension, bradycardia, or arrhythmia.
   c. **Neurologic manifestations.** Headache, perioral paresthesias spreading centrifugally to hands and feet, hot–cold dysesthesia, and insomnia.
   d. **Mechanism of toxicity** is from prolonged opening of sodium channels.
   e. **Diagnosis** is based on the clinical symptoms and history. Samples of fish can be sent out for high-performance liquid chromatography and mass spectrometry to detect ciguatoxin.
   f. **Treatment.** Supportive care, **mannitol** 1 g per kg IV over 30 minutes has been suggested as an effective treatment if given early; however, supporting studies are lacking. Complete recovery usually occurs within a few weeks, but fatigue and weakness may persist.
2. **Tetrodotoxin poisoning.**
   a. **Sources.** Ingestion of puffer or globefish. Although processing of fugu (puffer fish fillets) is licensed, puffer-fish poisoning accounts for more deaths than any other type of food poisoning in Japan.

b. **Systemic signs.** Vomiting, hypotension, and respiratory arrest.
c. **Neurologic manifestations.** Paresthesia of the perioral region and extremities followed by paralysis of voluntary and respiratory muscles.
d. **Mechanism of toxicity.** Blockade of sodium channels.
e. **Diagnosis.** History of puffer fish ingestion and clinical features. NCS show complete conduction block effect on myelinated nerve fibers and sparing of axons.
f. **Treatment.** Supportive care.

3. **Other toxins affecting ion channels.** Grayanotoxin (rhododendron and sodium channel opener), scorpion toxin (sodium channel opener), and saxitoxin (shellfish and sodium channel blocker).

C. Toxins affecting neuromuscular junction.

1. **Black widow spider venom.**
   a. **Sources.** Black widow spider (*Latrodectus mactans*).
   b. **Systemic signs.** Hypertension, nausea, diaphoresis, and restlessness.
   c. **Neurologic manifestations.** Diffuse muscle spasms and rigidity.
   d. **Mechanism of toxicity.** Increased release of neurotransmitters (e.g., acetylcholine and norepinephrine) followed by the depletion of transmitter stores.
   e. **Diagnosis.** History and clinical examination. Bite location may show a "target lesion" with a pale center surrounded by erythema.
   f. **Treatment.** IV opioids for pain control and benzodiazepines for muscle relaxation. In severe cases, antivenom (equine-based antiserum) can be given, but carries the risk of anaphylaxis: Pretreatment with diphenhydramine and having epinephrine at the bedside is recommended.
2. **Botulism.**
   a. **Sources.** Replicating *Clostridium botulinum*, and occasionally *Clostridium baratii* and *Clostridium butyricum*, produce distinctive botulinal neurotoxins (types A to G).
      (1) **Food.** Ingestion of food contaminated with preformed toxin.
      (2) **Infant.** Ingestion of foods (honey) contaminated with *C. botulinum* spores.
      (3) **Wounds.** Commonly in IV drug users, infected with *C. botulinum.*
   b. **Systemic signs.** Sore throat, dry mouth, vomiting, and diarrhea followed by abdominal distention and constipation.
   c. **Neurologic manifestations.** Descending motor paralysis including ophthalmoplegia, dysphagia, mydriasis (in 50%), skeletal, and respiratory muscles. In infant botulism, babies have constipation followed by a subacute progression of bulbar and extremity weakness (within 4 to 5 days) manifested by inability to suck and swallow, weakened cry, ptosis, and hypotonia, which may progress to generalized flaccidity and respiratory compromise.
   d. **Mechanism of toxicity** involves inhibition of presynaptic vesicles preventing the release of acetylcholine.
   e. **Diagnosis.**
      (1) **History and examination.** Difficult to differentiate from Miller Fisher syndrome, although ataxia, paresthesia, areflexia, and elevated CSF protein are more common in Miller Fisher syndrome. In infants, the differential diagnosis includes sepsis, viral syndrome, dehydration, diphtheria, cerebrovascular accident, hypothyroidism, hypermagnesemia, Lambert–Eaton's myasthenic syndrome, myasthenia gravis, poliomyelitis, Guillain–Barré's syndrome, encephalitis, and meningitis.
      (2) **Laboratory.** Confirmation of *C. botulinum* in serum, stool, gastric contents, wound culture, food specimens, or positive mouse bioassay.
      (3) **NCS.** Facilitation on repetitive nerve stimulation (in 60% of cases).
   f. **Treatment.**
      (1) Supportive care and antibiotics for wound botulism. In infant botulism, respiratory decompensation is associated with administration of aminoglycoside antibiotics and neck flexion during positioning for lumbar puncture or imaging. Antibiotics are not indicated for infant botulism.
      (2) **Botulinum antiserum** for food and wound botulism. Obtained from the Centers for Disease Control and Prevention by the state health departments.
      (3) For infant botulism, **human-derived IV botulinum immune globulin (BIG)** trials demonstrated safety and efficacy. BIG is now Food and Drug

Administration approved and is available only from the California Department of Health Services (24-hour telephone: 510-231-7600 or Webpage http://www.infantbotulism.org/).

3. **Other toxins affecting the neuromuscular junction** include the venom of the funnel web spider (increases acetylcholine release), saliva from the *Ixodid* family of ticks (prevents acetylcholine release), hypermagnesemia (prevents acetylcholine release), venom from cobra, coral snake, mamba, and Mojave rattlesnakes (decreases nicotinic neurotransmission by various mechanisms).

D. Myopathy.

1. **Immobility.** Toxins that depress mental status or produce coma can result in extended periods of immobility compressing muscular compartments causing subsequent muscle breakdown and rhabdomyolysis. Examples include alcohol, barbiturates, benzodiazepines, and narcotics.
2. **Excess activity.** Toxins, or activities, that result in skeletal energy consumption exceeding energy supply can cause rhabdomyolysis. This can be the direct effect of the drug or secondary to agitation. Examples include amphetamines, cocaine, phencyclidine (PCP), and anticholinergic drugs.
3. **Myotoxins.**
   a. **Hypokalemia.** Drugs depleting total body potassium stores can cause muscle breakdown and rhabdomyolysis. Examples include toluene and amphotericin B (renal tubular acidosis), glycyrrhizinic acid in licorice (increases mineralocorticoid activity), and long-term use of diuretics.
   b. **Metabolic poisons.** Compounds that interfere with the production of adenosine triphosphate can result in muscle breakdown and rhabdomyolysis. Examples include cyanide, hydrogen sulfide, salicylates, dinitrophenol, chlorophenoxy herbicides (2,4-D), and carbon monoxide (CO).
   c. **Direct-acting myotoxins.** Numerous agents exist that have direct toxic effects on muscles resulting in myopathy and rhabdomyolysis. Examples include ethanol, heroin, corticosteroids, antimalarials, HMG-CoA reductase inhibitors, and snake bites.

II. CENTRAL NERVOUS SYSTEM

A. Acute delirium.

1. **Anticholinergic syndrome** occurs from blockade of central and peripheral muscarinic receptors.
   a. **Sources.** Pharmaceuticals: tricyclic antidepressants, antihistamines, antipsychotics, class-1a antiarrhythmics, cyclobenzaprine, promethazine, benztropine, carbamazepine, amantadine, and scopolamine. Plants: jimson weed, nightshades, and mandrake.
   b. **Systemic signs.** Dry mouth, mydriasis, dry axilla, hypoactive bowel sounds, urinary retention, tachycardia, and low-grade fever.
   c. **Neurologic manifestations.** Acute delirium with visual hallucinations, increased motor activity (picking at bed sheets), and mumbling speech pattern.
   d. **Treatment.**
      (1) **Activated charcoal.** 1 g per kg by mouth if the patient is awake and is not at risk for aspiration and if ingestion is within 1 to 2 hours.
      (2) **Benzodiazepines.** Repeated IV doses for agitation and tachycardia.
      (3) **Butyrophenones** (haloperidol or droperidol) in addition to benzodiazepines for patients with severe agitation and acute psychosis (avoid in patients with a prolonged QT interval).
      (4) **Physostigmine.** May be useful as a diagnostic tool in differentiating anticholinergic syndrome from other neurologic causes (e.g., encephalitis). Because of its short half-life and potential complications, physostigmine is generally not recommended for treatment. The dosage is 1 to 2 mg slow IV push over 10 minutes. Complications are seizures, cardiac dysrhythmia, and cholinergic crisis. Contraindicated in the care of patients with unknown ingestions, bradycardia, or ingestions increasing risk of seizures (tricyclic antidepressants).
      (5) IV hydration and serial measurement of creatine kinase for rhabdomyolysis.

2. **Sympathomimetic syndrome.** Occurs from an increase in central and peripheral monoamines.
   a. **Sources.** Pharmaceuticals (pseudoephedrine, phenylpropanolamine, methylphenidate, and phentermine), illicit drugs (cocaine, amphetamines, methamphetamine, methylenedioxymethamphetamine), and plants (ma huang).
   b. **Systemic signs.** Tachycardia, hypertension, diaphoresis, mydriasis, fever, chest pain, myocardial infarction, and ventricular dysrhythmia.
   c. **Neurologic manifestations.** Psychomotor agitation, seizures, mania, tactile hallucinations (formication), increased muscle tone, increased reflexes with clonus, impaired cognition and chronic psychiatric symptoms, hyponatremia-induced cerebral edema, and ischemic or hemorrhagic stroke.
   d. **Treatment.**
      (1) **Activated charcoal.** 1 g per kg by mouth if the patient is awake and is not at risk for aspiration and if ingestion is within 1 to 2 hours.
      (2) **Benzodiazepines.** Repeat IV doses for seizures, agitation, tachycardia, hypertension, and chest pain. Avoid use of β-blockers secondary to unopposed α-stimulation and corresponding vasospasm.
      (3) **Butyrophenones** (haloperidol or droperidol) or atypical antipsychotics in addition to benzodiazepines for patients with severe agitation and acute psychosis.
      (4) IV **hydration** and serial measurement of creatine kinase for rhabdomyolysis.
      (5) Active **cooling** of hyperthermic patients.
3. **Serotonin syndrome.** Occurs from increase in extracellular concentrations of serotonin in the CNS. Typically occurs in patients taking more than one serotonergic agent.
   a. **Sources.** Pharmaceuticals (selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, meperidine, fentanyl, dextromethorphan, tramadol, venlafaxine, amphetamines, L-tryptophan, methylene blue, and lithium) and plants (St. John's wort).
   b. **Systemic signs.** Tachycardia, hypertension, diaphoresis, mydriasis, and hyperthermia.
   c. **Neurologic manifestations.** Agitation, confusion, hallucinations, increased motor tone and activity (lower more than upper extremity), and hyperreflexia with lower extremity clonus.
   d. **Treatment.**
      (1) **Activated charcoal.** 1 g per kg by mouth if the patient is awake and is not at risk for aspiration and if ingestion is within 1 to 2 hours.
      (2) **Benzodiazepines.** Repeat IV doses for agitation, tachycardia, and hypertension.
      (3) **Cyproheptadine,** a 5-HT2a antagonist, can be given orally, 12 mg as first dose, then 8 mg every 6 hours. Some **atypical antipsychotics** (olanzapine) may also be beneficial secondary to 5-HT2a antagonism and parenteral administration. Avoid when possibility of neuroleptic malignant syndrome exists.
      (4) IV hydration and serial measurement of creatine kinase for rhabdomyolysis.
4. **Hallucinogens.**
   a. **Sources.** Anticholinergic agents: see **II.A.1.a.** Illicit drugs (lysergic acid diethylamide, mescaline, PCP, and ketamine), plants (morning glory and nutmeg), mushrooms (*Amanita muscaria* mushrooms and psilocybin mushrooms), and animals (bufotoxin from *Bufo* family of toads).
   b. **Systemic signs.** Tachycardia, hypertension, diaphoresis, and mydriasis.
   c. **Neurologic manifestations.** Visual hallucinations, increased motor activity, and hyperreflexia.
   d. **Treatment.**
      (1) **Activated charcoal.** 1 g per kg by mouth if the patient is awake and is not at risk for aspiration and if ingestion is within 1 to 2 hours.
      (2) **Benzodiazepines.** Repeat IV doses as needed for agitation.
      (3) **Butyrophenones** (haloperidol or droperidol) in addition to benzodiazepines for patients with severe agitation and acute psychosis.
      (4) IV hydration and serial measurement of creatine kinase for rhabdomyolysis.
5. **γ-Aminobutyric acid (GABA)-agonist withdrawal syndromes** result in a hyperadrenergic state with symptoms similar to those of sympathomimetic syndrome.

a. **Benzodiazepines, barbiturates,** and **ethanol** can cause a life-threatening withdrawal syndrome characterized by a hyperadrenergic state (tachycardia, hypertension, diaphoresis, piloerection, and fever), nausea, vomiting, diarrhea, altered mental status, hallucinations, and seizures. Management of acute symptoms involves repeated IV doses of benzodiazepines (high doses at times) followed by scheduled oral benzodiazepines for prevention.
b. **Baclofen** can cause a life-threatening withdrawal syndrome characterized by disorientation, hallucinations, fever, rebound spasticity, seizures, and coma. Treatment involves oral or intrathecal baclofen and benzodiazepines.
c. **γ-Hydroxybutyrate (GHB).** Abrupt discontinuance of chronically abused GHB compounds results in a withdrawal syndrome similar to benzodiazepine and ethanol withdrawal. Treatment is with IV or oral benzodiazepines and supportive care.

6. Wernicke's encephalopathy.

a. **At risk populations** are persons with chronic alcoholism or patients with other thiamine deficiency states (e.g., hyperemesis gravidarum, anorexia nervosa, malignant tumor of the GI tract, pyloric stenosis, inappropriate parenteral nutrition, and in patients with gastric bypass surgery as early as 4 to 12 weeks postoperatively).
b. **Symptoms.** Characterized by altered mental status (global confusional state), ataxia, and ophthalmoplegia (nystagmus, sixth-cranial nerve palsy, conjugate palsy, vestibular paresis, and pupillary abnormalities). Although classically diagnosed with the triad of mental confusion (66% of patients), staggering gait (51% of patients), and ocular abnormalities (40% of patients), Wernicke's encephalopathy can occur in the absence of some or all of the symptoms.
c. **Diagnosis.** Clinical features and improvement with treatment. Laboratory assessments of thiamine deficiency include erythrocyte thiamine transketolase, the blood thiamine concentration, or urinary thiamine excretion (with or without a 5-mg thiamine load). Abnormal MRI findings are hyperintense signals in the dorsal medial thalamic nuclei, periaqueductal gray area, and the third and fourth ventricle, and mamillary body enhancement acutely and atrophy chronically. MRI has a sensitivity of 53% and a specificity of 93% for the diagnosis of Wernicke's encephalopathy. Treatment should be primarily based on clinical suspicion.
d. **Treatment.** IV thiamine (100 mg) and magnesium (2 g) followed by daily thiamine and multivitamin supplementation. Daily thiamine doses should be 50 to 100 mg for 7 to 14 days, then 10 mg per day until full recovery is achieved, followed by at least 1.2 mg per day.
e. **Prognosis** is favorable for most patients, but residual neurologic effects, including Korsakoff's psychosis, memory loss, ataxia, nystagmus, and neuropathy, may persist.

B. Subacute encephalopathy.

1. Bismuth. Long-term use of bismuth salts for ostomy odor or in the management of peptic ulcer disease can manifest as subacute progressive encephalopathy.

a. **Symptoms.** Patients have symptoms of progressive dementia and delirium, ataxia, severe myoclonus, and in rare instances, seizures. Symptoms may not occur until after weeks or years of continued use. Other symptoms include dark stools and dark staining of the gums. This syndrome can be mistaken for Creutzfeldt–Jakob's disease, Alzheimer's dementia, or other progressive forms of encephalopathy and can be fatal if not diagnosed.
b. **Diagnosis.** In acute encephalopathy, the bismuth blood level is 150 to 2,000 μg per 100 ml instead of the normal 10 to 30 μg per 100 ml. Head CT may show increased attenuation in the basal ganglia and cerebral cortex.
c. **Treatment.** Stop the drug and provide supportive care. The syndrome usually regresses in 3 to 12 weeks after cessation of bismuth.

2. Lithium. Chronic use or acute overdose of lithium salts can manifest as progressive encephalopathy. Impaired excretion or excessive intake of lithium are the usual causes of lithium intoxication.

a. **Symptoms.** Patients come to medical attention with tremor, altered mental status, ataxia, myoclonus, and in rare instances, seizures. Other symptoms include nausea, vomiting, diabetes insipidus, hypothyroidism, mutism, and renal failure.

b. **Diagnosis.** An elevated serum lithium level supports the diagnosis. Therapeutic levels of lithium range from 0.6 to 1.2 mEq per L. Toxic effects of lithium generally are related to serum levels, with mild to moderate severity seen with levels of 1.5 to 2.5 mEq per L, serious toxicity with levels of 2.5 to 3.0 mEq per L, and life-threatening toxicity with levels 3.0 to 4.0 mEq per L.

c. **Treatment.** Emesis or lavage and a cathartic are indicated in acute overdose. Patients with severe symptoms require urgent hemodialysis. Dialysis clears extracellular lithium but the intracellular lithium may cause a rebound in the serum lithium concentrations after dialysis. IV saline should be given to rehydrate and avoid hyponatremia (excretion of sodium and lithium are related).

3. **Carbon monoxide.** Patients with CO poisoning may have a syndrome known as **delayed neurologic sequelae,** occurring 2 to 40 days after exposure and recovery. The incidence of delayed neurologic sequelae increases with the duration of unconsciousness and age >30.

a. **Symptoms.** Manifested as altered mental status, personality changes, memory loss, and encephalopathy. Patients may also have ataxia, seizures, urinary and fecal incontinence, parkinsonism, mutism, cortical blindness, and gait and motor disturbances. Physical examination findings may include hyperreflexia, frontal release signs (glabellar and palmar grasp), masked facies, and parkinsonian features.

b. **Diagnosis.** Neuropsychometric testing displays cognitive dysfunction. MRI findings may include bilateral globus pallidus infarcts and diffuse demyelination of subcortical white matter.

c. **Treatment.** Supportive care. It is unclear whether treatment of acute CO poisoning influences the risk of delayed neurologic sequelae. The majority of patients will show some recovery.

4. **Aluminum.** Long-term use of aluminum phosphate binders, aluminum-contaminated dialysates or medications containing aluminum (e.g., sucralfate) in the care of patients with renal failure can result in progressive encephalopathy. Patients come to medical attention with agitation, speech disorder, confusion, myoclonus, coma, and/or seizures. Aluminum exposure is also associated with osteomalacia and microcytic hypochromic anemia. Diagnosis is made by elevated aluminum level but if within normal limits and diagnosis is still suspected, bone biopsy may confirm the diagnosis. Treatment involves removal of sources of aluminum and for some patients, chelation with deferoxamine.

5. **Neuroleptic malignant syndrome.** Subacute encephalopathy associated with hyperthermia, rigidity with elevated creatine kinase, and autonomic instability in the setting of neuroleptic administration. Treatment is supportive care with external cooling and benzodiazepines as necessary. Consideration can also be given to bromocriptine and/or dantrolene for antidotal therapy.

C. **Coma and CNS depression.** Many toxins causing CNS depression and coma can mimic brain death, including loss of brainstem reflexes. Many of these toxins have long half-lives, so clinical criteria of brain death do not apply.

1. **Sedative hypnotics.**

a. **Sources.** Ethanol, benzodiazepines, barbiturates, central-acting muscle relaxants, chloral hydrate, buspirone, zolpidem, baclofen, clonidine, antihistamines, and numerous antidepressants and antipsychotics.

b. **Systemic signs.** Pressure sores, hypotension, bradycardia, and hypothermia.

c. **Neurologic manifestations.** Somnolence, coma, areflexia, nystagmus, and amnesia.

d. **Treatment.** Supportive care, a**ctivated charcoal** 1 g per kg by mouth if the patient is awake and is not at risk for aspiration and if ingestion is within 1 to 2 hours. The use of **flumazenil,** a benzodiazepine antagonist, is generally **not recommended** because of increased risk of seizures in habituated patients.

2. **Opioids, opiates.**

a. **Sources.** Pharmaceuticals (hydrocodone, oxycodone, morphine, hydromorphone, oxymorphone, propoxyphene, meperidine, fentanyl, and methadone) and illicit drugs (heroin and designer opioids).

b. **Systemic signs.** Hypotension, bradycardia, bradypnea, pulmonary edema, track marks on skin, skin abscesses, decreased bowel sounds, and cyanosis.

c. **Neurologic manifestations.** Coma, miosis, deafness, areflexia, and seizures (meperidine and propoxyphene). Seizures from meperidine are the result of elevated levels of normeperidine (a major metabolite of meperidine). Risk factors for normeperidine seizures are renal failure and chronic dosing. Naloxone (Narcan; Endo Pharmaceuticals, Chadds Ford, PA, USA) does not reverse meperidine- or propoxyphene-related seizures.
d. **Treatment.** Supportive care, **Naloxone** 0.1 to 1 mg IV push followed by 1 mg every minute until reversal of respiratory depression or to a maximum of 10 mg (complications include acute opioid withdrawal).

3. GHB.
a. **Sources.** GHB, γ-butyrolactone, butanediol (used for mood enhancement, sleep induction, and by body builders for purported increased growth hormone release).
b. **Systemic signs.** Bradycardia, hypotension, hypothermia, nystagmus, and vomiting.
c. **Neurologic manifestations.** Areflexic coma (typically short duration—less than 6 hours with rapid reversal), normal or miotic pupils, and seizures.
d. **Treatment.** Supportive care.

4. Carbon monoxide.
a. **Sources.** Automotive exhaust, smoke inhalation, faulty heaters, external heating sources, propane- and gas-powered tools and vehicles.
b. **Systemic signs.** Tachycardia, hypotension, chest pain, dyspnea, myocardial infarction, cardiac arrhythmia, flushed skin, pressure sores, nausea, and vomiting.
c. **Neurologic manifestations.** Headache, confusion, cognitive deficits, coma, seizures, stroke, parkinsonism, and delayed neurologic sequelae (see **II.B.3.**).
d. **Diagnosis.** CO levels are indicative of exposure but are not reliable predictors of toxicity or symptoms. The normal result is <5% for nonsmokers and <10% for smokers.
e. **Treatment.**
(1) Removal from source of CO.
(2) 100% oxygen (via non-rebreather) for 6 to 12 hours for mild or moderate symptoms.
(3) **Indications for hyperbaric oxygen therapy.**
(a) Loss of consciousness; or
(b) Coma or persistent neurologic deficit; or
(c) Myocardial ischemia or ventricular dysrhythmia; or
(d) Hypotension or cardiovascular compromise; or
(e) Pregnancy with any of the above, levels >20%, or signs of fetal distress.

5. Cocaine or stimulant washout syndrome occurs among abusers of cocaine or other stimulants, the increased use of which decreases the level of CNS catecholamines resulting in depressed mental status, confusion, or coma (unresponsive to stimuli, including intubation). Patients may have disconjugate gaze. Other physical examination findings, vital signs, and laboratory findings generally are normal. Symptoms may last for 8 to 24 hours, and treatment is supportive. This should always be a diagnosis of exclusion.

D. Cerebellar disorders.

1. Toluene-solvent abuse syndrome.
a. **Sources.** Toluene-containing paint thinner, paint stripper, and glue.
b. **Route of exposure.** Inhalational: huffing (inhaling soaked rags) or bagging (inhaling from bags containing solvent).
c. **Systemic signs.** Abdominal pain, anorexia, weight loss, gastritis, possible renal tubular acidosis (hypokalemia and acidosis), rhabdomyolysis, hepatitis, and solvent odor on breath.
d. **Neurologic manifestations.** Tremor of the head and extremities, ataxia, staggering gait, cognitive deficits, personality changes, optic nerve atrophy, hearing loss, loss of smell, extremity spasticity, and hyperreflexia.
e. **Diagnosis.**
(1) **Laboratory.** Elevated serum toluene levels and urine hippuric acid levels confirm exposure, but may are not always detected.
(2) **Imaging.** MRI of the brain often shows cerebellar and cerebral atrophy. Evidence of white-matter disease can be seen with increased signal intensity on T2-weighted images in the periventricular, internal capsular, and brainstem pyramidal regions.

(3) **Electrophysiologic studies.** Brainstem auditory evoked response testing may show sparing of early components and loss or decrement of the late components (waves III and IV). Abnormal pattern visual evoked cortical potentials and prolonged P-100 peak latency may occur in patients with toxic optic neuropathy caused by toluene abuse.

f. **Treatment.** Supportive care and addiction rehabilitation.

2. **Mercury poisoning (see also section I.A.1.d.).** Poisoning with elemental mercury vapor or organic mercury along with other symptoms described in the previous section (I.A.1.d.) can result in cerebellar symptoms including ataxia and tremor with pathologic neuronal damage seen in visual cortex, cerebellar vermis and hemispheres, and postcentral cortex.
3. **Anticonvulsants** including phenobarbital, phenytoin, and carbamazepine, in elevated concentration or acute overdose, manifest with predominantly ataxia, nystagmus, and CNS depression. Chronic use of phenytoin may also result in cerebellar atrophy.
4. **Ethanol.** Both acute intoxication and chronic abuse of ethanol can result in ataxia, tremor, and altered mental status. Wernicke's encephalopathy should be considered when any patient with chronic alcoholism has changed mental status and ataxia not related to acute intoxication.

E. Parkinsonism.

1. **1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),** a byproduct in the production of a synthetic analog of meperidine, can cause acute parkinsonism in drug users, scientists, and pharmaceutical workers. Although not neurotoxic, MPTP is metabolized by monoamine oxidase to a compound that inhibits electron transport in dopaminergic neurons. This syndrome was characterized by the rapid (24 to 72 hours) development of end-stage parkinsonism with tremor, rigidity, bradykinesia, postural instability, masked facies, and decreased blink rate. Investigation of the mechanism of toxicity has led to the development of an animal model for Parkinson's disease.
2. **Manganese.** A parkinsonian-like illness has been described among miners or workers exposed to manganese oxide and among those who have ingested potassium permanganate, associated with methcathinone abuse. This syndrome is the result of degradation of the globus pallidus and striatum rather than the substantia nigra. It begins with a prodrome of nonspecific symptoms (insomnia, irritability, and muscle weakness) and progresses to psychiatric manifestations (hallucinations, emotional lability, and delusions) and finally to classic parkinsonian features of gait disturbance, masked facies, bradykinesia, rigidity, and less commonly tremor, which tends to be more postural or kinetic rather than resting. Patients with manganese-induced parkinsonism also experience dystonia consisting of facial grimacing and/or plantar flexion of the foot. These patients have little or no response to levodopa.
3. **Neuroleptic drugs.** The use of neuroleptic agents, both typical and atypical, has been associated with the acute development of extrapyramidal side effects, most commonly parkinsonism. Patient's age and duration and potency of neuroleptic treatment are risk factors for neuroleptic-induced parkinsonism. The presentation of neuroleptic-induced parkinsonism includes bradykinesia or akinesia, which may be associated with decreased arm swing, masked facies, drooling, decreased eye blinking, and soft, monotonous speech; tremor, which is most commonly a rhythmic, resting tremor; and rigidity of the extremities, neck, or trunk. Cessation of the neuroleptic typically results in resolution of symptoms within a few weeks. Patients can be treated with anticholinergics or dopaminergic agents although levodopa is not recommended because of insufficient efficacy and risk of exacerbating psychosis. Prolonged use of neuroleptics can result in tardive dyskinesia with choreiform movements of the face, tongue, and limbs. If recognized early, most symptoms of tardive dyskinesia resolve within 5 years.
4. **Mitochondrial toxins** (CO, **cyanide, and hydrogen sulfide).** Agents that inhibit the mitochondrial respiratory chain can cause development of bilateral globus pallidus infarction and subsequently a parkinsonian syndrome. This typically results from a combination of hypotension and hypoxia in severe poisoning and can have neuropsychiatric manifestations or more classic parkinsonism.

F. Seizures. Toxins cause seizures by one of four mechanisms: (1) decrease in the seizure threshold of a patient with an underlying seizure disorder, (2) direct effects on the CNS,

(3) withdrawal seizures, or (4) metabolic derangements. Most toxin-related seizures are generalized tonic–clonic. Most patients with toxin-induced seizures can be treated with standard seizure algorithms, except that treatment is more often successful with benzodiazepines and barbiturates then with phenytoin.

1. **Stimulants** (see also **II.A.2.**).
   a. **Sources.** Cocaine, amphetamines, methamphetamine, and PCP.
   b. **Mechanism of toxicity.** Secondary to increased levels of CNS catecholamines with subsequent excitation of the sympathetic nervous system. Can cause vasculitis, vasospasm, accelerated atherosclerosis and increase risk of both ischemic and hemorrhagic stroke.
   c. **Treatment.**
      (1) **Diazepam** 10 mg or **lorazepam** 2 mg IV, repeat doses as needed, or
      (2) **Phenobarbital** 20 mg per kg IV at rate of 25 to 50 mg per minute.
2. **Cholinergics** (see also **I.A.3.**)
   a. **Sources.** Organophosphate and carbamate insecticides and chemical warfare agents.
   b. **Mechanism of toxicity.** Increased CNS concentration of acetylcholine with secondary release of glutamate.
   c. **Treatment.**
      (1) **Diazepam** 10 mg, **lorazepam** 2 mg IV, repeat doses as needed, or **phenobarbital** 20 mg per kg IV at rate of 25 to 50 mg per minute for seizures.
      (2) **Atropine** 2 to 4 mg IV for signs of cholinergic excess.
      (3) **Pralidoxime** 1.5 g IV over 30 minutes for nicotinic symptoms.
3. **GABA antagonists.**
   a. **Sources.** Tricyclic antidepressants, phenothiazines, flumazenil, chlorinated hydrocarbons, hydrazines, cephalosporins, ciprofloxacin, imipenem, penicillins, isoniazid, steroids, clozapine, olanzapine, cicutoxin (water hemlock), picrotoxin (fish berries), and wormwood (absinthe).
   b. **Mechanism of action.** Direct or indirect inhibition of $GABA_A$ receptors or decreased synthesis of GABA through inhibition of either glutamic acid decarboxylase or pyridoxal kinase (e.g., isoniazid and hydrazines).
   c. **Treatment.**
      (1) **Diazepam** 10 mg, **lorazepam** 2 mg IV, repeat doses as needed, or **phenobarbital** 20 mg per kg IV at rate of 25 to 50 mg per minute for seizures.
      (2) **Pyridoxine.** For isoniazid or hydrazine overdose. The amount of pyridoxine administered should be equivalent (gram for gram) to the estimated amount of isoniazid ingested. It can be given IV push to patients with severe symptoms or as an IV infusion. If an unknown amount of isoniazid has been ingested, 5 grams IV can be given empirically.
4. **Glutamate agonists.**
   a. **Sources.** Domoic acid (shellfish), ibotenic acid (*A. muscaria* mushrooms), and *ß-N*-oxalylamino-L-alanine (BOAA found in legumes of the genus *Lathyrus*).
   b. **Mechanism of action.** Direct agonists at glutamate receptors (*N*-methyl-D-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid).
   c. **Other clinical features.** Patients with lathyrism from BOAA have spastic paraplegia.
   d. **Treatment.**
      (1) **Diazepam** 10 mg or **lorazepam** 2 mg IV for seizures, repeat doses as needed or **phenobarbital** 20 mg per kg IV at rate of 25 to 50 mg per minute.
5. **Antihistamines.**
   a. **Sources.** First-generation (sedating) antihistamines (diphenhydramine, chlorpheniramine, and brompheniramine).
   b. **Mechanism of action.** Central histamine-1 receptor antagonism.
   c. **Other clinical features.** See anticholinergic syndrome (**II.A.1.**).
   d. **Treatment.**
      (1) **Diazepam** 10 mg or **lorazepam** 2 mg IV for seizures, repeat doses as needed, or **phenobarbital** 20 mg per kg IV at rate of 25 to 50 mg per minute.
6. **Adenosine antagonists.**
   a. **Sources.** Theophylline, caffeine, theobromine, pentoxifylline, and carbamazepine.
   b. **Mechanism of action.** Antagonism of presynaptic A1 receptors preventing

inhibition of glutamatergic neurons, and A2 receptors causing cerebral vasoconstriction. Theophylline may decrease GABA levels by decreasing pyridoxal-5-phosphate levels.

c. **Other clinical features.**
   (1) The manifestations of theophylline toxicity are similar to those of sympathomimetic syndrome (see **II.A.2.**).
   (2) The manifestations of carbamazepine toxicity are similar to those of anticholinergic syndrome (see **II.A.1.**).

d. **Treatment.**
   (1) **Phenobarbital** 20 mg per kg IV at rate of 25 to 50 mg per minute for altered mental status, CNS agitation, theophylline levels >100 µg per ml, or seizures, additionally may use repeated doses of **diazepam** 10 mg or **lorazepam** 2 mg as needed.
   (2) **Hemodialysis** for theophylline or caffeine overdose with seizures.

7. Withdrawal seizures.

a. **Sources.** Ethanol, benzodiazepines, barbiturates, and baclofen.

b. **Mechanism of action.** Prolonged use of GABA agonists results in decreased activity at GABA receptors and increased activity at glutamate receptors.

c. **Other clinical features.** Delirium, hallucinations, tachycardia, hypertension, fever, autonomic instability, and hypertonicity (baclofen).

d. **Treatment.**
   (1) **Diazepam** 10 mg or **lorazepam** 2 mg IV for seizures, repeat doses as needed, or **phenobarbital** 20 mg per kg IV at rate of 25 to 50 mg per minute.
   (2) For **baclofen** withdrawal oral baclofen should be restarted at the previous rate, or the baclofen pump should be refilled.

Recommended Readings

Albers J. Toxic neuropathies. *Continuum*. 1999;5:27–50.

Albin RL. Basal ganglia neurotoxins. *Neurol Clin*. 2000;18(3):665–680.

Dobbs MR. *Clinical Neurotoxicology. Syndromes, Substances, Environments*. Philadelphia, PA: Saunders Elsevier; 2009.

Flomenbaum NE, Goldfrank LR, Hoffman RS, et al., eds. *Goldfrank's Toxicologic Emergencies*. 8th ed. New York, NY: McGraw-Hill; 2006.

Ibrahim D, Froberg B, Wolf A, et al. Heavy metal poisoning: clinical presentations and pathophysiology. *Clin Lab Med*. 2006;26(1):67–97, viii.

Kao LW, Nanagas KA. Carbon monoxide poisoning. *Med Clin North Am*. 2005;89(6):1161–1194.

O'Connor AD, Rusyniak DE, Bruno A. Cerebrovascular and cardiovascular complications of alcohol and sympathomimetic drug abuse. *Med Clin North Am*. 2005;89(6):1343–1358.

Rusyniak DE, Nanagas KA. Organophosphate poisoning. *Semin Neurol*. 2004;24(2):197–204.

Rusyniak DE, Sprague JE. Hyperthermic syndromes induced by toxins. *Clin Lab Med*. 2006;26(1):165–184, ix.

Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. 2nd ed. New York, NY: Oxford University Press; 2000.

Walsh RJ, Amato AA. Toxic myopathies. *Neurol Clin*. 2005;23(2):397–428.

Wills B, Erickson T. Drug- and toxin-associated seizures. *Med Clin North Am*. 2005;89(6):1297–1321.

CHAPTER

55 Sleep Disorders

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Sleep disturbances are prevalent in the general population, but certain groups such as older adults, women, and patients with chronic comorbid medical, neurologic, and psychiatric disorders are at particular risk. Indeed, the most recent evidence points to a bidirectional relationship between health and sleep. Sleep problems influence health-related quality of life and may contribute to the development of, or exacerbate, medical and neurologic conditions. Patients who report disturbed sleep generally describe one or more of three types of problems—insomnia, excessive daytime sleepiness (EDS), and abnormal motor activities, complex behaviors, or disturbed sensations during sleep.

The 2005 revised *International Classification of Sleep Disorders* (*ICSD-2*) lists five major categories of sleep disorders: insomnias—that is, disorders of initiating and maintaining sleep; sleep-related breathing disorders; hypersomnias—that is, disorders of excessive sleepiness; movement disorders; and circadian rhythm sleep disorders (CRSDs). To assist the clinician, in diagnosing and treating sleep disorders, a differential diagnosis-based classification adapted from the *ICSD-2* is used in this chapter.

I. INSOMNIA

Insomnia is a disorder characterized by symptoms of inability to fall asleep, maintain sleep, perception of inadequate sleep, and/or nonrestorative sleep. These symptoms result in distress or impairment of daytime functioning. The three main categories of insomnia are psychophysiologic insomnia, idiopathic insomnia, and paradoxical insomnia (state misperception).

A. Psychophysiologic and idiopathic insomnias.

1. **Course.** For the diagnosis of psychophysiologic insomnia to be made, a patient has to have sleep difficulties that substantially affect daytime functioning and have a learning or conditioning component that typically involves one or more of the following: daily worries about not being able to fall asleep or stay asleep accompanied by intense efforts to fall asleep each night; paradoxical improvement away from the usual sleep environment (e.g., in another room of the house or away from home); and somatized tension and anxiety associated with bedtime and the subject of sleep. The most difficult differential diagnosis is with generalized anxiety disorders in which anxiety is pervasive and involves most aspects of daily life rather than exclusively the inability to sleep. Differentiation from affective disorders, such as depression, is also important. Idiopathic or primary insomnia is a lifelong inability to sleep, presumably associated with a predisposition for insomnia resulting from abnormality of the sleep–wake cycle or autonomic activity. Patients with this condition are a heterogeneous group. Most have been poor sleepers since childhood, and the insomnia, although it persists over the entire life span, can be aggravated by stress and tension. Patients with idiopathic insomnia may have atypical reactions to stimulants and sedatives. Idiopathic insomnia often is accompanied by other factors such as poor sleep hygiene or psychiatric disorders. Therefore, there tends to be some overlap between primary insomnia with insomnia that is comorbid with psychiatric disorders.
2. **Treatment and outcome.** A multimodal individualized approach is indicated for most patients. Optimizing the treatment of comorbid medical, neurologic, and psychiatric conditions, as well as identifying medications or behaviors that promote insomnia are essential first steps. A combined treatment approach involving good sleep hygiene, cognitive behavioral therapy (CBT), and medications is most often employed. A 4- to 8-week program of sleep hygiene counseling, cognitive/behavioral modifications, and judicious

use of hypnotics is recommended. If insomnia does not improve after this period of treatment, referral to a sleep specialist should be considered for further evaluation.

a. **Cognitive behavioral therapy.** The most widely used behavioral therapy program in the management of insomnia includes a combined program of sleep hygiene education, relaxation techniques, stimulus-control therapy, and sleep restriction therapy. Relaxation techniques may include progressive muscle relaxation, biofeedback, deep breathing, meditation, guided imagery, and other techniques to control cognitive arousal. These techniques are first taught during training sessions and then practiced daily for 20 to 30 minutes by the patient at home, usually around bedtime. **Stimulus-control therapy** is useful in the management of conditioned insomnia. This technique is an attempt to break the conditioning by teaching the patient to associate the bedroom with sleep behavior. The instructions for sleep hygiene and stimulus-control behavioral therapy are listed in Tables 55.1 and 55.2. Sleep restriction therapy involves curtailment of time in bed, so that sleep efficiency (time asleep divided by time in bed) is 85% or greater. As sleep efficiency increases, time in bed is gradually lengthened. Shorter duration behavioral interventions and internet-based CBT are also available.

b. **Hypnotic drugs.** The most widely used prescription hypnotics are the benzodiazepine receptor agonists, which include benzodiazepines and the non-benzodiazepine receptor agonist (BZRA) hypnotics, such as eszopiclone, zaleplon, and zolpidem. Traditionally, this class of medications was indicated for short-term use. More recently, with the recognition that insomnia is often chronic and with the availability of longer term studies for up to a year, the short-term indication has been removed from the newly The U.S. Food and Drug Administration (FDA)-approved BZRA

TABLE 55.1 Sleep Hygiene Instructions

Homeostatic drive for sleep
Avoid naps, except for a brief 10- to 15-min nap 8 hr after arising; check with your physician first, because in some sleep disorders naps can be beneficial
Restrict sleep period to average number of hours you have actually slept per night in the preceding week. Quality of sleep is important. Too much time in bed can decrease quality on the subsequent night
Get regular exercise every day, preferably 40 min in the afternoon. It is best to finish exercise at least 3 hr before bedtime
Take a warm bath 90 to 120 min before bedtime to help lower body temperature
Circadian factors
Keep a regular out-of-bed time (do not deviate >1 hr) 7 d a week
Do not expose yourself to bright light if you have to get up at night
Expose yourself to bright light, either outdoor or artificial, during the day
Drug effects
Do not smoke to get yourself back to sleep
Do not smoke after 7:00 p.m.; give up smoking entirely
Avoid caffeine and limit caffeine use to no more than three cups no later than 10:00 a.m.
Avoid alcoholic beverages after 7:00 p.m.
Arousal in sleep setting
Keep clock face turned away, and do not find out what time it is when you wake up at night
Avoid strenuous exercise after 6:00 p.m.
Do not eat or drink heavily for 3 hr before bedtime. A light bedtime snack may help
If you have trouble with regurgitation, be especially careful to avoid heavy meals and spices in the evening. You may have to raise the head of your bed
Keep your room dark, quiet, well ventilated, and at a comfortable temperature
Use a bedtime ritual. Reading before lights-out may be helpful if it is not occupationally related
Do not try too hard to sleep; instead, concentrate on the pleasant feeling of relaxation
Use stress management and relaxation techniques in the daytime
Be sure your mattress pillow is of the right height and firmness
Use the bedroom only for sleep; do not work or do other activities that lead to prolonged wakefulness

TABLE 55.2 Stimulus-Control Behavioral Therapy

Go to bed only when sleepy. Stay up until you are really sleepy, and then return to bed. If sleep still does not come easily, get out of bed again. The goal is to associate bed with falling asleep quickly
Use the bed only for sleeping. Do not read, watch television, or eat in bed
If unable to sleep, get up and move to another room
Repeat the preceding step as often as necessary throughout the night
Set the alarm and get up at the same time every morning, regardless of how much you slept during the night. This helps the body acquire a constant sleep–wake rhythm
Do not nap during the day

TABLE 55.3 FDA Approved Hypnotics for the Management of Insomnia

Agent	Dose (mg)	Onset of Action (min)	Half-Life (hr)	Active Metabolites
Benzodiazepine receptor agonists (benzodiazepines)				
Triazolam (Halcion)	0.125–0.25 (0.125)	15–30	2–5	No
Temazepam (Restoril)	15–30 (7.5–15)	45–60	8–20	No
Estazolam (ProSom)	1–2 (0.5–1.0)	15–60	8–24	No
Flurazepam (Dalmane)	15–30 (7.5)	0.5–1 hr	47–100 including metabolites	Yes
Quazepam (Doral)	7.5–15 (7.5)	20–45	15–40 including metabolites	Yes
New generation benzodiazepine receptor agonists				
Zolpidem (Ambien)	5–10	Short	2.8	None
Zolpidem-CR (Ambien)	6.25–12.5	Short	2.9	None
Zaleplon (Sonata)	5–10	Ultrashort	1	None
Eszopiclone (Lunesta)	1–3	Intermediate	5–7	Yes
Melatonin receptor agonist				
Ramelteon (Rozerem)	8	Short	2.6	Yes
H1 receptor antagonist				
Doxepin (Silenor)	3–6	Long	15.3	

hypnotics such as eszopiclone and zolpidem MR. Ramelteon, a melatonin receptor agonist and low-dose doxepin, represent different classes of hypnotics that in the nonscheduled category.

The choice of hypnotic may depend on the type of insomnia. For example, if the predominant problem is falling asleep, a fast-acting, short-half-life hypnotic may be preferable. If the problem is frequent awakenings and sleep maintenance insomnia, a longer acting hypnotic may be more effective. Most hypnotics approved by the FDA are indicated for the treatment of sleep onset insomnia, whereas eszopiclone, zolpidem-CR and low-dose doxepin are also indicated for the treatment of sleep maintenance insomnia. In practice, sedating antidepressants, such as the tricyclic antidepressants and heterocyclics (trazodone), are often used off label for the treatment of insomnia. However, there is limited data regarding their efficacy or long-term safety for the treatment of insomnia that is not comorbid with depression. The exception is low-dose doxepin (3 to 6 mg), which is FDA approved for insomnia.

The most widely used prescription hypnotics and their properties are listed in Table 55.3. Although patients with chronic insomnia rarely become "great" sleepers

after treatment, most can manage the predisposition to insomnia by using sleep hygiene, cognitive behavioral treatment, and when indicated hypnotics.

B. Paradoxical insomnia.

1. **Course.** It is not uncommon for patients to overestimate sleep latency and underestimate total sleep time. In paradoxical insomnia, this tendency is extreme.
2. **Diagnosis.** The disorder is characterized by reports of persistent difficulty falling, staying asleep or disturbed sleep, although sleep duration and quality are objectively normal.
3. **Treatment and outcome.** Reassuring patients with the fact that their sleep is normal and that they sleep longer than they think they do and cognitive behavioral treatments are effective.

C. Insomnia associated with psychiatric disorders.

1. **Course.** Insomnia is often comorbid with psychiatric conditions. Results of epidemiologic studies suggest that as many as 57% of persons with insomnia have a psychiatric condition or will have one within 1 year. The comorbid condition usually is a mood disorder, anxiety disorder, somatoform disorder, personality disorder, schizophrenia, or substance abuse. Sleep in major depression is characterized by early morning awakening (2 to 4 hours after sleep onset) and frequent nocturnal awakening with inability to reinitiate sleep. Insomnia often precedes the diagnosis of depression. The incidence of insomnia among patients with anxiety disorders is high. The typical symptoms are difficulty with sleep initiation and, to a lesser degree, nocturnal awakenings. Fatigue is common, but napping is unusual. Patients with anxiety disorders are susceptible to conditioning factors that produce psychophysiologic insomnia.
2. **Treatment and outcome.** Treatment should address the comorbid psychiatric disorder as well as insomnia. For major depressive and anxiety disorders, this involves use of antidepressants or anxiolytics such as the selective serotonin reuptake inhibitors (SSRIs). An antidepressant with sedative properties is favored over a less-sedating one for patients with insomnia. Administration 30 minutes before bedtime also aids in promoting sleep. Amitriptyline, trimipramine, doxepin, trazodone, and mirtazapine are the most sedating, whereas protriptyline and SSRIs such as fluoxetine have stimulating effects that may worsen insomnia. Antidepressants with anxiolytic properties are useful in the treatment of anxious, depressed patients and facilitate psychotherapeutic or pharmacologic treatment. Anticholinergic side effects of tricyclic antidepressants (cardiotoxicity, urinary retention, erectile dysfunction, and dry mouth) limit the usefulness of these agents, particularly in the elderly.

   Recent studies demonstrate that insomnia may persist despite adequate treatment of depression and that insomnia predicts future relapse of depression. Therefore, oftentimes, a parallel approach that combines treatment for both depression and insomnia is recommended. If the patient is refractory to treatment, referral to a sleep specialist or psychiatrist is recommended for further evaluation of comorbid psychiatric or other sleep disorders.

II. CIRCADIAN RHYTHM SLEEP DISORDERS

Circadian rhythms are generated by a neural clock located in the suprachiasmatic nucleus of the hypothalamus. Disruption of biologic timing results in circadian rhythm disorders that are most often associated with patients' reports of insomnia and excessive sleepiness. **CRSDs** are characterized by essentially normal total sleep time that is not synchronized with conventional environmental light–dark cycles and periods of sleep. Diagnosis requires specialized assessment, including use of a sleep diary for 7 days alone, or in combination with actigraphy, physiologic markers of circadian timing such as core body temperature or melatonin onset. A careful history interview to elicit the appropriate major diagnostic criteria is a key. CRSDs include delayed sleep phase disorder (DSPD), advanced sleep phase disorder (ASPD), non-24-hour sleep–wake disorder, irregular sleep–wake rhythm disorder, (ISWR) shift work sleep disorder (SWSD), and jet lag disorder. Effective treatment for CRSDs typically require a multifaceted approach to realign circadian rhythms with the use of timed bright light exposure and low-dose melatonin, together with cognitive behavioral treatments

that promote healthy sleep habits. Melatonin is not approved by the FDA for the treatment of CRSDs, and one should also be aware of potential side effects such as headaches, vivid dreams, nausea, and cardiovascular effects.

A. DSPD and ASPD.

1. **Course. DSPD** is characterized by a persistent inability to fall asleep until the early morning hours (1 to 3 a.m., and sometimes later) and difficulty waking up in the morning. If allowed, the patient would sleep until the late morning or early afternoon (10 a.m. to 2 p.m.). When the patient is forced to rise at 7 or 8 a.m., sleep is curtailed, and daytime sleepiness develops. Despite the daytime sleepiness, patients find that in the evening they become more alert and remain unable to fall asleep until the early morning hours. The prevalence rate is estimated to be between 1.7% in the general population to 7% of those with insomnia complaints. Onset of this disorder typically occurs during adolescence or early adulthood. **ASPD** is characterized by early evening sleep onset (7 to 9 p.m.) and early morning awakening (3 to 5 a.m.). Although DSPD predominates at younger ages and ASPD at older ages, both disorders can result in sleep problems throughout life. Because many features of the sleep of patients with depression resemble those of either DSPD or ASPD, depression and other psychiatric disorders must be considered in the differential diagnosis.
2. **Treatment and outcome.**
   a. **Chronotherapy is** a behavioral technique in which bedtime is systematically delayed (for DSPD) or advanced (for ASPD) in 3-hour increments each day until the desired sleep phase is achieved. The patient is then instructed to maintain the newly established bedtime rigidly. Although this approach works, it is an arduous procedure, and maintenance of the effect has been difficult.
   b. **Bright light therapy.** Light intensity >2,500 lux is considered bright. Appropriately timed bright light (white or blue/green enriched) exposure can reset the timing of circadian rhythms, and normalize circadian phase in DSPD and ASPD. Exposure to bright light in the early morning results in an advancement of circadian phase, whereas exposure to light in the evening delays circadian rhythms. For management of DSPD, exposure to light usually is scheduled for 1 to 2 hours in the morning (close to the time of habitual awakening). For ASPD, light exposure is recommended in the evening, approximately 2 to 4 hours before scheduled bedtime. Avoidance of bright light in the evening in DSPD should also be encouraged. Despite high rates of success in achieving the desired sleep phase under immediate treatment, many patients do not continue the light regimen and have a relapse. Some patients are able to maintain a normalized phase without maintenance of light exposure for as long as several months, whereas others drift back toward the pretreatment phase within a few days.
   c. **Melatonin** has been shown to shift the phase of circadian rhythms in humans. Although not approved by the FDA, melatonin of 1 to 5 mg has been shown to be effective when taken in the early evening for patients with DSPD.

B. Free-running disorder (FRD).

1. **Course.** Individuals with FRD typically have a longer than 24-hour circadian rhythm, similar to those living in temporal isolation. Because these patients are unable to entrain to the external 24-hour physical, social or activity cycles, sleep and wake periods progressively drift later each day. Diagnosis of FRD includes complaints of insomnia or excessive sleepiness associated with the misalignment between the endogenous circadian rhythm and the light-dark cycle. FRD is most common in blind people, but can occur in sighted persons.
2. **Treatment and outcomes.** Both behavioral and pharmacologic options are available for the treatment of FRD, depending on whether the patient is sighted or blind. For blind and sighted patients, planned sleep schedules and/or low-dose melatonin (0.5 to 3 mg) approximately 1 to 2 hours before habitual bedtime are recommended. In sighted persons, the addition of timed exposure to bright light is also recommended.

C. Irregular sleep wake rhythm disorder.

1. **Course.** ISWR differs from the phase disorders in that there is loss of circadian rhythmicity, which results in the lack of a long, consolidated sleep period. Sleep usually is broken into three or more short sleep periods or naps during the course of 24 hours.

Irregular sleep–wake patterns occur among patients with Alzheimer's disease and among other elderly persons in nursing homes.

2. **Treatment and outcomes.** Management of irregular sleep–wake patterns and associated behavioral problems in this group of elderly and often cognitively impaired patients is a challenge. Treatment with sedative-hypnotics is prevalent in nursing homes. These medications have side effects that may not be well-tolerated by older patients. Some promising studies have indicated that structured activity programs, increasing exposure to bright light and evening melatonin may alleviate these sleep–wake and behavioral disorders. The effects of melatonin have been mixed, and a recent placebo-controlled multicenter study in Alzheimer's disease failed to demonstrate its effectiveness. Light therapy units are commercially available.

E. SWSD.

1. **Course.** SWSD is characterized by chronic symptoms of insomnia and excessive sleepiness that are due to unconventional work schedules, resulting in circadian misalignment. Typically, sleep is curtailed by 1 to 4 hours in patients with SWSD, with most complaints associated with night and early morning work. Excessive sleepiness at work and commute poses important safety concerns.
2. **Treatment and outcomes.** Clinical management of SWSD is aimed at realigning circadian rhythms with the sleep and work schedules, as well as improving sleep, alertness, and safety. Nonpharmacologic treatments are basic to the management of SWSD. Optimizing the sleep environment, adherence to healthy sleep habits, and planned naps, when possible, should be encouraged for all patients.
   a. **Bright light therapy.** Timed bright light therapy and avoidance of light at the wrong time of the day can help accelerate and maintain entrainment to the shift schedule. For night workers, circadian rhythms need to be delayed, so that the highest sleep propensity occurs during the day, rather than at night. Intermittent bright light exposure (approximately 20 minutes per hour blocks) and avoidance of bright light exposure in the morning during the commute home (using driving safe sunglasses) has being shown to accelerate circadian adaptation to night shift.
   b. **Melatonin.** Studies on the effectiveness of melatonin for the treatment of SWSD have been mixed. When taken at bedtime after the night shift, melatonin can improve daytime sleep; it may have limited effects on alertness at work. Other pharmaceuticals often used for the treatment of sleep disturbance and excessive sleepiness in shift workers includes: hypnotics for sleep and stimulants for maintaining alertness. However, these approaches do not specifically address the issue of circadian misalignment, and thus should be used in concert with behavioral strategies as discussed above.

III. DISORDERS OF EXCESSIVE DAYTIME SLEEPINESS

Sleepiness severe enough to affect activities of daily living is estimated to be present among 30% of the population and is most commonly caused by self-imposed restriction of sleep. However, approximately 4% to 5% of the population has EDS as a result of a sleep disorder. Sleepiness is excessive and an indication of a sleep disorder when it occurs at undesirable times, such as while driving and during social activities. EDS can be divided into two types: extrinsic and intrinsic. Some extrinsic causes include environmental factors, drug dependency, sleep-disordered breathing, and movement disorders during sleep. The more common types of intrinsic hypersomnia usually associated with primary CNS includes disorders such as narcolepsy and idiopathic hypersomnia.

A. Narcolepsy.

1. **Course.** Narcolepsy is a manifestation of dissociation between wakefulness and sleep, particularly rapid eye movement (REM) sleep. The onset usually occurs in adolescence or young adulthood, and men are affected more often than are women. Studies have shown a strong genetic association between narcolepsy and the human leukocyte antigen (HLA) type DR2 and DQ1. A more sensitive marker for narcolepsy is the DQB1*0602 genotype, which appears to be correlated with both the frequency and severity of cataplexy (loss of muscle tone elicited by a strong emotional response).

The role of hypocretin in narcolepsy is supported by the finding that hypocretin levels are abnormally low or undetectable in the CSF of most narcoleptic patients. Values below 110 pg per ml are highly diagnostic for narcolepsy in the absence of severe brain pathology. The most consistent abnormalities were observed in the amygdala, where increased dopamine and metabolite levels were found.

2. **Clinical features.** Narcolepsy is a syndrome characterized by a pentad of severe unremitting EDS manifesting as sleep attacks, cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations and disturbed nocturnal sleep. Some patients will also have other comorbid primary sleep disorders such as restless legs and REM sleep behavior disorder (RBD; see next section). All patients must have pathologic levels of daytime sleepiness, and the presence of unequivocal cataplexy, a feature pathognomonic for narcolepsy. Cataplexy is associated with a drop in H-reflex and loss of skeletal muscle and is induced by strong emotional stimuli. Decreased quality and quantity of nocturnal sleep exacerbate the EDS even further.

B. Classification of narcolepsy.

1. **Narcolepsy with cataplexy.** Characterized by EDS and bona fide cataplexy. Sleepiness is maximal during monotonous activities and may appear as irresistible sleep attacks.
2. **Narcolepsy without cataplexy.** Narcolepsy without cataplexy is similar to narcolepsy with cataplexy in most clinical respects except for the lack of definite cataplexy.
3. **Narcolepsy caused by a medical condition.** Narcolepsy with and without cataplexy is found in a number of key medical and neurologic conditions including genetic disorders associated such as type Prader–Willi's syndrome, structural lesions in the hypothalamic region, and inflammatory lesions such as multiple sclerosis and acute disseminated encephalomyelitis.
4. **Diagnosis.** In addition to the clinical history, nocturnal polysomnography (PSG) and multiple sleep latency testing (MSLT) are performed to establish a diagnosis of narcolepsy.
   a. *Sleep studies.*
      (1) **PSG.** A baseline sleep study is generally required for an accurate diagnosis of narcolepsy because of the spectrum of conditions that can cause excessive sleepiness. Most typically, the nocturnal PSG is required, followed by the MSLT. PSG features of narcolepsy include sleep disruption, repetitive awakenings, and decreased REM sleep latency. A sleep-onset REM period (SOREMP) at night is highly predictive of narcolepsy.
      (2) **The MSLT.** The MSLT during the day following the PSG and is designed to determine a patient's propensity to fall asleep. Current criteria for narcolepsy include a mean sleep latency (MSL) ≤8 minutes and ≥2 SOREMPs. Up to one-third of the general population may have an MSL of ≤8 minutes so the finding of a short MSL alone, without any SOREMP, should be interpreted cautiously together with the clinical picture.

      If the results of sleep studies are inconclusive, results of HLA typing and CSF hypocretin (below 110 pg per ml) may provide additional aid in establishing the diagnosis.
5. **Treatment and outcome.** Treatment approaches to narcolepsy emphasize control of narcoleptic symptoms to allow optimal social and professional productivity by maintaining the patient's alertness throughout the day. Choice of treatment must take into account that narcolepsy is a lifelong disorder and that patients will have to take medications for many years. Clinicians are not unanimous in their approach to management of narcolepsy.
   a. The drugs commonly used to manage EDS and sleep attacks are the nonamphetamine stimulants such as armodafinil and modafinil and **CNS stimulants** including, methylphenidate, and dextroamphetamine. Because of frequent side effects of sympathomimetic stimulants, such as irritability, tachycardia, elevated blood pressure, and nocturnal sleep disturbance, methylphenidate and amphetamines are probably less preferred first-line treatment. Armodafinil and modafinil has several advantages over other stimulants in that it has fewer cardiovascular side effects, has longer half-life, and can be taken one daily in the morning, and the prescription can be refilled. Sodium oxybate has been recently approved for the management of symptoms of hypersomnia and cataplexy in narcolepsy. Medications used in the management of

EDS and the dosages are listed in Table 55.4. Drugs with norepinephrine-releasing properties have the greatest impact on sleepiness. However, evidence shows that even at the highest recommended doses, no drug is capable of returning a person with narcolepsy to a normal baseline level of alertness.

b. The management of abnormal REM-intrusion phenomenon such as cataplexy, sleep paralysis, and hypnagogic hallucinations involves sodium oxybate and **tricyclic antidepressant medications.** Sodium oxybate is currently approved for the management of cataplexy and daytime sleepiness in narcolepsy. Protriptyline and clomipramine have been used widely, often with good results. Other tricyclic medications, such as imipramine, desipramine, and amitriptyline, are also effective; however, anticholinergic side effects (particularly erectile dysfunction) limit the ability of many patients to tolerate these medications, particularly if high doses are needed to control cataplexy. Fluoxetine is somewhat less effective for cataplexy, but it has the advantage of being a mild stimulant (Table 55.4). An example of an initial regimen for narcolepsy among adults is provided in Table 55.5.

c. A third approach to the management of narcolepsy is to **improve the nocturnal sleep** of persons with narcolepsy. Improvement of nocturnal sleep not only decreases EDS but also may help cataplexy. Nocturnal sleep disturbances may be related to periodic limb movements of sleep (PLMS), which frequently occur among patients with narcolepsy. They may, however, also be a complication of treatment with stimulants and tricyclic medications. Management of PLMS with dopamine agonist drug (ropinirole and pramipexole) may be helpful.

d. **Nonpharmacologic treatment.** Scheduled short "power" naps and support therapy must be emphasized. Short naps of 15 to 20 minutes three times during the day help maintain alertness and have been shown to have a recuperative power in narcoleptic subjects.

(1) **Drug holiday.** In cases of tolerance, switching to a different class of medication or providing a drug holiday for 1 to 2 days can be useful.

(2) **Psychosocial considerations.** Patients with narcolepsy often experience social and professional difficulties owing to sleepiness and cataplexy. Narcolepsy can result in unemployment, rejection by friends, and depression. For these reasons, it is important to encourage patients with narcolepsy to join support groups, as the Narcolepsy Network (http://www.narcolepsynetwork.org/) and to provide referral for psychotherapy when needed.

6. **Side effects of stimulant medications.** The amphetamine-like medications are typically associated with side effects such as hypertension, alterations in mood, and psychosis. Moreover, tolerance and, less frequently, addiction may be observed with drugs such as amphetamines. Interestingly, with high dosages of amphetamines (100 mg per day), a paradoxic effect of increased sleepiness may result. This paradoxic effect disappears with reduction of the daily dosage. Other common side effects include increased jitteriness, verbal aggressiveness, "racing thoughts," increased heart rate, tremor, and involuntary movements. The most commonly reported side effects of the nonamphetamine stimulants, armodafinil, and modafinil includes headache, gastrointestinal (GI) irritability, nausea, and the potential to interact and lower the efficacy of oral contraceptives. Side effects associated with sodium oxybate include disorientation in the middle of the night and morning grogginess, enuresis, and nausea at the time of initiating the medication and at higher doses.

C. Hypersomnia other than narcolepsy.

1. **Course.** This group of disorders characterizes patients whose diagnosis does not meet that of narcolepsy but is associated with severe disabling hypersomnia without the associated cataplexy, which is unique with narcolepsy. The age at onset varies from adolescence to middle age. The symptoms are life-long, with some potential for improvement if an associated condition is identified.
2. **Clinical features.** Patients report sleepiness throughout the day associated with prolonged naps, which unlike narcolepsy, are not refreshing. Automatic behaviors and some features of REM sleep intrusion (such as hypnogogic hallucinations) may occur during periods of drowsiness. These behaviors often are inappropriate, and patients usually do not have any recollection of these events. Patients have severe difficulty awakening in the morning.

TABLE 55.4 Medications Used to Treat CNS Hypersomnias

Medication Name	Medication Class	Usual Daily Dose Range	Usual Starting Regimen	FDA Approval	FDA Pregnancy Category	Special Considerations
Amphetamine/ dextroamphetamine	Amphetamines	10–60 mg	10 mg daily	Yes	C	Black box warning—abuse
Dextroamphetamine		5–60 mg	5 mg b.i.d.	Yes	C	Same as above
Methamphetamine		5–60 mg	10 mg daily	No	C	Same as above
Methylphenidate	Amphetamine-like	10–60 mg	5 mg b.i.d.	Yes	C	Black box warning—dependence
Mazindol		3–8 mg	2 mg b.i.d.	No	Unknown	
Pemoline		18.75–112.5 mg	37.5 mg daily	No	B	Not used due to liver toxicity
Modafinil	Non-amphetamine stimulants	100–400 mg	200 mg daily	Yes	C	Requires barrier contraception
Armodafinil		150–250 mg	150 mg daily	Yes	C	Requires barrier contraception
Sodium oxybate	Sedative-hypnotic	4.5–9 g	2.25 g × 2	Yes	B	Short half life
Protriptyline	Tricyclic antidepressants	5–30 mg	5 mg daily	No	C	Black box warning—suicidality

Medication Name	Medication Class	Usual Daily Dose Range	Usual Starting Regimen	FDA Approval	FDA Pregnancy Category	Special Considerations
Imipramine		25–150 mg	25 mg daily	No	D	Same as above
Clomipramine		25–125 mg	25 mg daily	No	C	Same as above
Fluoxetine	SSRI	10–40 mg	20 mg daily	No	C	Same as above
Selegiline	Monoamine oxidase inhibitors	5–10 mg	20 mg daily	No	C	
Venlafaxine	Serotonin-norepinephrine reuptake inhibitor	75–225 mg	37.5 mg daily	No	C	Black box warning—suicidality
Atomoxetine	Norepinephrine reuptake inhibitors	40–80 mg	40 mg t.i.d.	No	C	Same as above
Bupropion	Norepinephrine-dopamine reuptake inhibitor	200–450 mg	100 mg b.i.d.	No	C	Same as above
Ritanserin	Type-2 serotonin (5-HT2) receptor-antagonist	5–10 mg	5 mg daily	No	Unknown	

Adapted from Wise MS, Arand DL, Arger RR, et al. Treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30(12):1712–1727.
Abbreviations: b.i.d., twice a day; t.i.d., three times a day.

TABLE 55.5 Example of an Initial Treatment Plan for Narcolepsy in Adults

Avoidance of shifts in sleep schedule
Avoidance of heavy meals and alcohol intake
Regular timing of nocturnal sleep: 10:30 p.m. to 7:00 a.m.
Naps. Strategically timed naps, if possible (e.g., 15 min at lunchtime and 15 min at 5:30 p.m.)
Medication. The effects of stimulant medications vary widely among patients. The dosing and timing of medications should be individualized to optimize performance. Additional doses, as needed, may be suggested for periods of anticipated sleepiness
Armodafinil (150–250 mg daily upon awakening), modafinil: 200 mg/d (200 mg on awakening or 100 mg b.i.d.)
If difficulties persist: may increase modafinil to 400 mg/d
Methylphenidate: 5 mg (three or four tablets) or 20 mg SR in morning (on empty stomach)
If difficulties persist:
methylphenidate (SR): 20 mg in morning
5 mg after noon nap
5 mg at 4:00 p.m.
If no response:
Dexedrine spansule (SR): 15 mg at awakening
5 mg after noon nap
5 mg at 3:30 or 4:00 p.m. (or 15 mg at awakening and 15 mg after noon nap)

3. **Examples of hypersomnia other than narcolepsy.**
   (a) **Recurrent hypersomnia.** The recurrent hypersomnias are very rare conditions in which patients experience prolonged episodes of severe sleepiness separated by periods of normal alertness and function. Recurrent hypersomnia presents as two distinct clinical forms: With the *Kleine–Levin's syndrome* (KLS), which usually affects adolescent males, patients may sleep for all but a few hours daily for periods lasting from days to weeks. The hypersomnia in KLS is often accompanied by variable disturbances of mood, cognition, and temperament, often including increased appetite and significantly aggressive or hypersexual behavior. *Menstrual-associated hypersomnia* is a poorly characterized condition in which episodic sleepiness coincides with the menstrual cycle; it is postulated to be secondary to hormonal influences.
   (b) **Hypersomnia caused by a medical condition.** *Hypersomnia here may be* diagnosed when sleepiness is thought to be the direct result of a medical or neurologic condition, but the patient does not meet clinical or laboratory criteria for a diagnosis of narcolepsy. A variety of conditions may underlie this disorder including associated neurologic disorders such as encephalitis, cerebrovascular accidents, brain tumor, head trauma, and Parkinson's disease. Common genetic conditions associated with sleepiness include Prader–Willi's syndrome and myotonic dystrophy.
4. **Diagnosis.** The differential diagnosis includes narcolepsy and primary sleep disorders such as sleep-disordered breathing or PLMS, which may also be associated with significant daytime sleepiness. Therefore, the diagnosis is made by means of elimination of other causes of daytime sleepiness. PSG should be performed to further assess these possibilities, and MSLT should be performed to document the level of objective daytime sleepiness.

   Mean sleep latencies are often <8 minutes but unlike narcolepsy, which is diagnosed electrographically when the MSL is <8 minutes and when two or more SOREMP are present, the criteria for the latter must include less than two SOREMS and an equally short sleep latency.
5. **Treatment and outcome.** Because multiple etiologic factors and because of the relative lack of understanding of the underlying pathophysiologic mechanism, treatment is symptomatic and the response is variable. Behavioral therapies and sleep hygiene instructions should be recommended but have only modest positive effect. The only medications that provide partial relief of excessive sleepiness are stimulant-like drugs. The most commonly suggested medications are armodafinil, modafinil, sodium

oxybate, methylphenidate, and dextroamphetamine. Tricyclic antidepressants, SSRIs, clonidine, bromocriptine, amantadine, and methysergide have been used with varying success. Sometimes combinations of these drugs yield better control of sleepiness. Even with the highest recommended dose, complete control of daytime sleepiness is seldom achieved in this group of patients. Therefore, prescribing >400 mg of modafinil, >60 mg of methylphenidate, or 40 mg of dextroamphetamine does not provide significant additional symptomatic relief. The patient should be advised not to drive or engage in potentially dangerous activities that require high levels of alertness. Pemoline was recently withdrawn in the United States due to its potential hepatotoxicity (see Table 55.4). Treatment for patients with KLS includes the amphetamine and nonamphetamine stimulants, and mood stabilizers such as lithium, valproic acid, and carbamazepine.

IV. PARASOMNIA

Parasomnia is a group of disorders that occur during sleep, are associated with wake-to-sleep transition, or are associated with arousal from sleep. These conditions with important consideration in neurology include RBD, sleepwalking (somnambulism), night terrors, nightmares, confusional attaches, and nocturnal frontal lobe epilepsy. The ones that are most often encountered in adult clinical practice are discussed.

A. Non-REM parasomnia. Sleepwalking and sleep terrors are episodic behaviors that occur as arousals from non-REM stages of sleep, usually when the patient is coming out of slow-wave sleep. Because sleepwalking (somnambulism) and sleep terrors (pavor nocturnus) among adults are most often associated with each other, the key features are discussed together.

1. **Course.** The prevalence of sleepwalking and sleep terrors is estimated at approximately 6% of the population. These types of parasomnia are most frequent among children and often disappear by adolescence. These behaviors may be considered normal among children, but for a large number of persons, they persist into adulthood. Patients may report a family history of parasomnia.
2. **Clinical features.** During these episodes, patients will exhibit polymorphic motor behaviors, such as talking, sitting up, and getting up to walk. These episodes have the potential to become dangerous because patients may bump into walls and windows or fall down stairs. With sleep terrors, extreme autonomic discharge culminating with screaming is a unique feature. Patients usually have only vague recollections of these events and are confused or agitated if awakened.
3. **Diagnosis.** For adults, thorough evaluation of abnormal nocturnal behavior should be performed to differentiate non-REM parasomnias from other pathologic entities, particularly nocturnal seizures.
4. **Treatment and outcome.** Therapy for non-REM parasomnia includes several approaches consisting of preventive measures, psychological interventions, and medications (Table 55.6).
   a. **Preventive measures and psychological intervention.** Preventive measures are taken to avoid serious injury during episodes of sleepwalking. The patient should be advised to locate the bedroom on the first floor, lock windows and doors, cover windows and glass doors with heavy draperies, and remove hazardous objects from the house.

      Hypnosis and psychotherapy have also been used in the management of parasomnia. Hypnosis has been shown helpful, at least for a short time, to young adults. The need for psychotherapy depends on the association of psychological factors with the parasomnia. Psychotherapy has been used most widely to treat young adults for sleep terrors. Most cases of parasomnia increase in severity and frequency with psychological stress. Therefore, in addition to psychotherapy, relaxation programs, such as progressive muscle relaxation and biofeedback, may be beneficial. Anticipatory awakening has been reported as a treatment modality for sleepwalking and perhaps other disorders of arousal. The technique involves waking the patients between 15 and 30 minutes prior to the time of the typical episodes.

TABLE 55.6 Treatment for Most Common Non-REM Parasomnias

	Treatment
Confusional arousal	Reassurance when benign in nature Avoid precipitants such as: –Sleep deprivation –Alcohol –CNS depressants Escitalopram (10 mg)—*for sexsomnia*
Somnambulism (sleep walking)	Safeguard the sleep environment and protect the patient Avoid precipitants: –Sleep deprivation –Lithium –Nonbenzodiazepines receptor agonists (i.e., zolpidem) Anticipatory awakenings Benzodiazepines –Clonazepam (0.5–1 mg) –Diazepam (10 mg) –Triazolam (0.25 mg) Imipramine (50–300 mg)
Sleep terrors	Reassurance when benign in nature CBT Progressive muscle relaxation Biofeedback Hypnosis Psychotherapy Pharmacotherapy: –Paroxetine (20–40 mg) –Clonazepam (0.5–1 mg)

b. **Medications.** The benzodiazepines—most commonly clonazepam, alprazolam, and diazepam—have been used. In the management of sleep terrors, tricyclic antidepressants (particularly imipramine) have been used either alone or in combination with benzodiazepines to provide control of symptoms. In addition, several studies have shown that treatment with carbamazepine may be beneficial. An example of an initial therapeutic approach is to start with clonazepam (0.25 to 1.0 mg) approximately 30 minutes before bedtime. If the response is inadequate, the dose should be increased by balancing the side effects, which include confusion and daytime drowsiness, particularly in the care of the older adult. A secondary line of treatment includes initiation of low doses of tricyclic antidepressant drugs or carbamazepine at bedtime.

Results of management of non-REM parasomnia are poorly documented. However, the little information in the literature indicates that response to combinations of pharmacologic and nonpharmacologic therapies is excellent. After various lengths of time, as many as 70% of adult patients report disappearance of the symptoms.

B. RBD.

1. **Course.** REM sleep and dreaming is normally accompanied by muscle atonia. RBD is characterized by the loss of REM-sleep atonia or excessive motor activation during sleep. Patients with this disorder most commonly report vigorous sleep behaviors that are accompanied by vivid dreams. These behaviors may be quite violent and can result in serious injury. RBD occurs in both acute and chronic forms. The **acute form** usually is associated with toxic–metabolic etiologic factors, most commonly, drug withdrawal states, particularly delirium tremens. Loss of REM atonia may also occur among patients taking medications that suppress REM sleep, such as tricyclic antidepressants and fluoxetine, and substances such as caffeine. The **chronic form** usually occurs among older adults. It has been seen in association with various brainstem abnormalities, extrapyramidal neurologic

disorders, and medical conditions (α-synucleopathies such as Parkinson's disease and Parkinson's plus syndrome [Shy–Drager's syndrome, multiple systems atrophy, Lewy's body dementia], brainstem stroke, brainstem tumor, demyelinating disease, and medication toxicity or withdrawal [i.e., SSRI, alcohol]) or is idiopathic. The differential diagnosis of RBD includes non-REM parasomnias, severe obstructive sleep apnea (OSA; "pseudo RBD"), periodic movements of sleep, nocturnal seizures, and nocturnal rhythmic movements. It is important to recognize this condition and differentiate it from other nocturnal behaviors because RBD can be managed effectively. The condition may precede the onset of the neurodegeneration by a few years-to-decades and may be a predictor of an evolving synucleinopathy.

2. **Treatment and outcome.** Management of RBD involves validation of the condition and counseling light of the possible association with dementia, pharmacologic therapy and interventions that address issues concerning environmental safety.
   a. The most commonly prescribed **drug therapy** is clonazepam at a dosage of 0.5 to 1.0 mg at bedtime. Clonazepam may be taken earlier (1 to 2 hours before bedtime) by patients who report sleep-onset insomnia or morning drowsiness as a result of the medication. If patients have significant OSA associated with RBD, they should be treated with continuous positive airway pressure (CPAP) because Clonazepam may potentially exacerbate OSA. Clonazepam is effective in 90% of cases, and there is little evidence of abuse and infrequent in tolerance in this group of patients. Beneficial effects are observed within the first week of treatment. Typically, treatment with clonazepam results in control of vigorous, violent sleep behaviors, but mild to moderate limb movement, sleep talking, and other complex behaviors may persist. Discontinuation of treatment usually results in recurrence of symptoms. More recently, melatonin (3 to 12 mg per q.h.s.) has been shown to be useful in improving dream enactment behavior and even restoring muscle atonia. This treatment has the advantage of relative lack of sedation, cognitive impairment, and lack of respiratory suppression. There have been few reported cases of successful treatment with dopamine agonists; pramipexole was 0.5 to 1 mg, dopamine precursors, and antiepileptic agents. Table 55.7 depicts a list of treatment options for RBD with the respective level of evidence based on a recent literature review. Both melatonin and clonazepam appear to have the strongest level of evidence in the management of this condition.
   b. **Environmental safety** is an important issue in the management of RBD. Patients should be advised to remove potentially dangerous objects from the house, to pad hard and sharp surfaces around the bed, to cover windows with heavy draperies, and even to place the mattress on the floor to avoid falling out of bed. The combination of drug therapy and implementation of safety precautions offers safe and effective management of RBD.

TABLE 55.7 Treatment of RBD

	Dose	Level of Recommendation
Clonazepam	0.25–4.0 mg q.h.s., usual recommended dose = 0.5–2.0 mg 30 min before bedtime	Suggested
Melatonin	3–12 mg q.h.s.	Suggested
Pramipexole	0.125 mg starting dose with effective dose ranging from 0.5 to 1.5 mg nightly	
Paroxetine	10–40 mg	May be considered
Donepezil	10–15 mg	May be considered
Rivastigmine	4.5–6 mg b.i.d.	May be considered
Temazepam	10 mg	May be considered
Alprazolam	1–3 mg	May be considered
Yi-Gan San	2.5 gm t.i.d.	May be considered
Desipramine	50 mg q.h.s.	May be considered
Carbamazepine	500 to 1,500 mg q.d.	May be considered
Sodium oxybate	Unknown	May be considered

c. Nocturnal seizures should be considered in the differential diagnosis of many forms of parasomnias. If the history suggests a seizure disorder or if symptoms are not controlled, **referral** to a neurologist or sleep specialist for further evaluation is recommended. Sometimes, a referral to a movement disorders/cognitive specialist may be indicated if patient present with motor findings, dementia, and behavioral disturbances.

V. MOVEMENT DISORDERS OF SLEEP

A. Restless legs syndrome (RLS) and PLMS.

1. **Course.** RLS is characterized by creeping, crawling, and disagreeable sensations in the lower and occasionally in the upper extremities associated with irresistible movements of the extremities. The symptoms are present at rest (quiesogenic) and are relieved by movements such as stretching, rubbing, and walking. Lying down in bed and falling asleep is a major problem for patients with RLS. Dysesthesia and the need to move the lower extremities are the most severe at bedtime and are often associated with sleep-initiation insomnia, which is indeed the most common reason for presentation. Many patients also report severe dysesthesia and leg jerks in the middle of the night with difficulty returning to sleep.

Up to 80% of patients with RLS also have periodic limb movement disorder (PLMD). However, PLMD can occur without RLS and has its own diagnostic category. Unlike RLS, which is a clinical diagnosis, PLMD is suspected when a patient or bed partner reports repeated leg kicks and is confirmed by periodic limb movements in the PSG. The typical PSG findings consist of stereotyped repetitive rhythmic movements. The leg movement must last for 0.5-to-10 seconds, and candidate leg movements are considered "periodic" if three or more occur with their onsets separated by 5 to 90 seconds. The legs movements consist of dorsiflexion of the foot, and occasionally may also involve the upper extremities. PLMD usually is more frequent during the first half of the night but can be present throughout sleep. Movements may be associated with sleep disruption. If numerous, the movements can result in nocturnal awakenings and EDS. The prevalence of PLMD increases with age, from 5% among those younger than 50 years to 44% among those 65 years and older.

For most patients with RLS or PLMD, the cause is unknown and therefore termed **idiopathic.** In many cases, RLS is familial and has an autosomal dominant inheritance with a significant genome-wide association with a common variant in an intron of BTBD9 on chromosome 6p21.2. Both RLS and PLMD have recently been shown to be associated with anemia resulting from iron deficiency, particularly when the ferritin level is <45 mcg per L. Folic acid, vitamin B_{12} deficiency, neuropathy, myelopathy, rheumatoid arthritis, thyroid dysfunction, and uremia have also been shown to have an association. Results of studies suggest that RLS is associated with alteration in CSF ferritin levels. Furthermore, PLMD may be induced or exacerbated by SSRIs and tricyclic antidepressants as well as by withdrawal from a variety of hypnotic agents. The existence of these conditions should be entertained in the differential diagnosis of PLMD so that patients receive the appropriate therapy. If these conditions are suspected, referral to the appropriate specialist is recommended.

2. **Treatment.** The four major classes of drugs that have been shown to be effective in the management of RLS are dopaminergic drugs, benzodiazepines, anticonvulsants, and opioids. Common medications used in the treatment of RLS are shown in Table 55.8.
   a. The first approach for patients with symptoms consistent with RLS symptoms is to draw a serum ferritin level. Patients with levels <45 mg per L should begin iron replacement therapy with iron sulfate along with vitamin C to improve absorption.
   b. When iron stores are normal, nonergotamine dopamine (D_2 D_3) agonists such as ropinirole and pramipexole may be started. Dopamine agonists are preferred because they are specifically FDA approved for the treatment of RLS. Major side effects include unpredictable sleep attached, GI side effects, postural orthostatic hypotension, and at higher doses, very rare cases of compulsive behaviors such as compulsive gambling.

TABLE 55.8 Pharmacotherapy for RLS

Drug: Class (Generic/Brand)	Dose	Risks
Iron:		GI side effects: constipation.
Ferrous sulfate	325 mg b.i.d./t.i.d. Recommended for ferritin levels <50 mcg	Role in treatment under current investigation
Dopamine agonists:		Severe sleepiness, nausea reported in some cases. Nausea, vomiting, sleep attacks, rare compulsive gambling
Pramipexole (Mirapex)[a]	Start low and increase slowly 0.125–0.5 mg, 1 hr before bedtime	
Ropinirole (Requip)[a]	0.25–2 mg 1 hr before bed time	
Dopaminergic agents:		Nausea, sleepiness, augmentation of daytime symptoms, insomnia, sleepiness, GI disturbances
Levodopa/cardidopa (Sinemet)	25/200 mg: ½ tab–3 tabs 30 min before bedtime	
Anticonvulsants:		Daytime sleepiness, nausea somnolence/sedation and dizziness. May cause driving impairment
Gabapentin (Neurontin)	300–2,700 mg/d divided t.i.d.	
Gabapentin enacarbil (Horizant)[a]	600 mg/d taken with food at about 5:00 p.m.	
Benzodiazepines:		Nausea, sedation, dizziness
Clonazepam (Klonopin)	0.125–0.5 mg ½ hr before bedtime	
Clonidine:	0.1 mg b.i.d.	Dry mouth, drowsiness, constipation, sedation, weakness, depression (1%), hypotension
Catapres	May be helpful in patients with hypertension	
Opioids:		Nausea, vomiting, restlessness, constipation. Addiction, tolerance may be possible
Darvocet (Darvoset-N)	300 mg/d	
Darvon (Propoxyphene)	65–135 mg at bedtime	
Codeine	30 mg	

[a]FDA approved drugs for RLS as of October, 2011.

c. Historically carbidopa/levodopa (at a dose of 25 per 100 mg q.h.s.) was initially widely used. However, its wide use is limited due to the risk of rebound symptoms as well as augmentation decreased. Carbidopa/levodopa is given at bedtime, and the dosage is increased progressively until a therapeutic effect is obtained. Usually a dose of carbidopa/levodopa (50 per 200 mg) is sufficient to control RLS and PLMD.

A second administration during the day may be necessary if patients report an increase in leg movements in the morning. Treatment with controlled-release carbidopa/levodopa (Sinemet CR) may also alleviate the rebound effect. Additional side effects include dysesthesia or leg movements during the day. Dyskinesia associated with long-term levodopa treatment, as observed among patients with Parkinson's disease, are uncommon in this group of patients.

d. The **anticonvulsant** gabapentin (starting with 100 to 300 mg), either alone or in combination with the dopamine agonist medications, also relieves the symptoms of RLS and PLMD. The FDA has very recently approved gabapentin enacarbil extended-release. Tablets for the treatment of moderate-to-severe primary RLS in adults.

e. Several **benzodiazepines,** including clonazepam, nitrazepam, lorazepam, and temazepam, have been found to improve the nocturnal sleep of patients with RLS and PLMS. Of these, clonazepam is the most widely used. The therapeutic action of clonazepam most likely results from its ability to decrease the number of arousals caused by leg movements. The usual starting dosage of clonazepam is 0.5 to 1.0 mg at bedtime for management of PLMS. Management of RLS may require additional doses to control symptoms during the day. Because benzodiazepines are CNS depressants, they may aggravate sleep apnea, particularly among older persons.

f. Finally, **opioids** are highly effective in the management of RLS and PLMS. In severe cases refractory to other treatments, intermittent therapy with opioids provides good relief. Other proposed treatments include carbamazepine, clonidine, and baclofen.

VI. SLEEP-DISORDERED BREATHING

The most commonly encountered types of abnormal nocturnal breathing are the sleep apnea and hypopnea. Sleep apnea is cessation of breathing for at least 10 seconds caused by obstruction of the upper airway (OSA), loss of respiratory effort or rhythmicity (central apnea), or a combination of the two (mixed apnea). Hypopnea is a decrease in airflow, which can be obstructive or central in origin. Many patients with sleep apnea have combinations of the central and obstructive types, which suggest that the mechanisms of the different types of sleep apnea may overlap.

A. Central sleep apnea (CSA).

1. **Course.** Patients with CSA constitute <10% of all patients with sleep apnea who undergo studies in sleep laboratories. Therefore, only a few studies have been reported, which limits knowledge of this disorder. Little information is available regarding the cardiovascular sequelae of CSA. The most common finding is sinus arrhythmia with bradycardia. Oxygen desaturation in patients with CSA tends to be generally mild to moderate compared with that in patients with OSA. Although the cause of CSA in most cases is unknown, it has been associated with certain diseases that should be considered in the differential diagnosis and management of this disorder. These diseases include central alveolar hypoventilation (Ondine's curse), obesity hypoventilation (Pickwickian) syndrome, congestive heart failure (Cheyne–Stokes' breathing pattern), autonomic dysfunction (Shy–Drager's syndrome, familial dysautonomia, and diabetes mellitus), neuromuscular disorders (muscular dystrophy, myasthenia gravis, and motor neuron disease), and brainstem lesions.
2. **Treatment** of patients with CSA is limited and not satisfactory. Studies regarding treatment usually have involved small numbers of patients, and very few have addressed the long-term efficacy of the proposed treatments.
   a. One approach is noninvasive nocturnal ventilation delivered by means of a nasal mask with a volume- or pressure-cycled ventilator. This approach is used to manage only the most severe cases of central alveolar hypoventilation or in the care of patients with neuromuscular disorders.
   b. For patients with medical or neurologic conditions known to be associated with CSA, the condition should be managed specifically and the central apnea reassessed. However, if the problem persists or if a cause is not found, several pharmacologic agents can be used. Acetazolamide, a carbonic anhydrase inhibitor, has been shown to improve CSA. In a small number of patients, acetazolamide has been shown to

reduce substantially the number of episodes of central apnea. The recommended dosage is 250 mg four times a day. Even fewer studies address the long-term efficacy of this treatment. The side effects associated with mild metabolic acidosis usually are well-tolerated by this group of patients.

c. Other medications, such as theophylline, naloxone, and medroxyprogesterone acetate, have been used with varying degrees of success. Tricyclic antidepressants, particularly clomipramine, have been used successfully to treat a small number of patients. Because none of these medications has been studied systematically, more precise recommendations regarding their use are currently not available.

d. Some patients with CSA have been shown to benefit from therapy with nasal CPAP. This type of therapy is most beneficial to obese patients who also have signs of upper airway obstruction with predominantly central apnea. Nasal CPAP has also been shown effective in the treatment of patients with congestive heart failure in whom central apnea and periodic breathing are observed during sleep. Finally, oxygen therapy has been useful in managing central apnea.

Adaptive seroventilation (ASV). It provides a relatively low baseline pressure and variable ventilatory support to establish a preset level of ventilation for each breath. If the patient's effort decreases, the ASV's inspiratory support increases to maintain a steady level of ventilation. This treatment is indicated in patients with CSA, but also OSA patients are refractory to standard CPAP. Some sleep experts have established the term complex sleep apnea referring to patients with OSA who develop CSA on initiation of CPAP. These patients with so-called treatment-emergent central apneas often experience spontaneous resolution of their disease with ongoing therapy.

B. OSA.

1. **Course.** The initial symptoms of OSA syndrome are loud snoring, excessive sleepiness, fatigue, morning headaches, memory problems, alterations in mood, and episodes of apnea witnessed by the bed partner. OSA is associated with considerable morbidity, including sleep fragmentation, daytime sleepiness that may lead to vehicular and industrial accidents, nocturnal hypoxemia, and cardiovascular as well as cerebrovascular sequelae (e.g., stroke, right heart failure, and hypertension). OSA is generally caused by upper airway obstruction resulting from obesity and skeletal and soft-tissue abnormalities. Examination of the nose and throat may indicate a possible cause. However, some patients with OSA may have normal findings at physical examination.

   If OSA is suspected, PSG should be performed to ascertain the severity of the breathing disorder, which will determine the appropriate therapy. Some patients who have symptoms indistinguishable from those of OSA may have predominantly sleep hypopnea. Sleep hypopnea syndrome should be managed in the same manner as sleep apnea syndromes.

   The **apnea–hypopnea index (AHI)** (number of respiratory events per hour of sleep) is used to measure sleep-disordered breathing. An index of 5 is generally accepted as the upper limit of the normal range. An AHI >20 has been shown to result in increased mortality. Therefore, all patients with indexes >20 should be treated. Patients who have milder indexes but whose respiratory events are accompanied by more significant oxygen desaturations and who have additional cardiovascular risk factors such as hypertension, history of heart disease, high cholesterol level, and cigarette smoking also should be treated.

2. **Therapy.** The approach to management of OSA and hypopnea syndromes involves both general measures and interventions that address specific abnormalities. For most patients, nasal CPAP is the most effective medical therapy for control of sleep apnea.

   a. **General measures** for identifying and addressing coexistent lifestyle issues that exacerbate OSA should be part of treatment of all patients. Although difficult to achieve, weight loss is an important factor in the treatment of obese persons with apnea. Sleep apnea generally improves with weight loss and may even be improved with weight loss of 40 to 50 pounds (18 to 23 kg). In addition to dietary control, this approach requires an exercise program and psychological counseling for long-lasting results. Unfortunately, results indicate that most patients regain the weight within 2 years. If sleep-disordered breathing is more prominent in the supine position, positional

therapy to avoid sleep in the supine position is very useful. Alcohol, hypnotic drugs, and other CNS depressant drugs interfere with the arousal response that terminates apneic episodes. Therefore, patients should avoid alcohol use and should not take hypnotics or sedatives. If a specific cause for upper-airway obstruction is found, an otorhinolaryngologic or maxillofacial evaluation is recommended for possible surgical intervention and trials of orthodontic devices, including tonsillectomy or adenoidectomy for enlarged tonsils or adenoids and correction of retrognathia or micrognathia. Results indicate that dental devices may be useful to those patients with mild-to-moderate sleep apnea with some degree of retrognathia or micrognathia. If chronic rhinitis is found, nasal steroid sprays may be beneficial.

b. **Nasal CPAP.** If no specific cause of upper airway obstruction is found, nasal CPAP is the treatment of choice. This treatment is effective for most patients with obstructive apnea and hypopnea. The level of CPAP should be determined by means of titration of the therapeutic pressure in a sleep laboratory, respiratory data being obtained in all sleep stages. Nasal CPAP requires patency of the nasal airway. Therefore, this procedure may not be effective for patients with severe nasal obstruction. The most common causes of intolerance of nasal CPAP are nasal symptoms, dryness, discomfort from the mask, and social and psychological factors of having to use the mask during sleep (due to claustrophobia). Added humidification often alleviates dryness and associated nasal congestion. With higher pressures, bilevel positive airway pressure (BiPAP) may be a more comfortable alternative to CPAP. Most home care companies provide both nasal CPAP and BiPAP services. If a patient with sleep apnea also has low baseline oxygen saturation during the day or during sleep, referral to an internist or pulmonologist is recommended. Although improvement of symptoms, including daytime sleepiness, may be observed within 1 or 2 days of treatment with nasal CPAP, maximal improvement may not occur for several weeks. Follow-up studies indicate that long-term compliance with nasal CPAP is a substantial problem for many patients not using CPAP throughout the night and on a daily basis. Compliance increases with close follow-up care. Follow-up visits should be scheduled 1 month after the start of CPAP and every 6 months thereafter. The Centers for Medicare & Medicaid Services (CMS) has recently issued a memo that authorized payment for CPAP may take place only if formal PSG was performed and was diagnostic for OSA, and that CMS will be pay for CPAP therapy for 3 months (and subsequently if OSA improves) for adults diagnosed with either PSG or with unattended home sleep monitoring devices. The use of portable home monitoring devices may improve access to diagnosis and treatment of OSA. However, these devices must be used as part of a comprehensive sleep evaluation program that includes access to board-certified sleep specialists, PSG facilities, and therapists experienced in fitting and troubleshooting CPAP devices.

c. **Oxygen therapy.** Oxygen has been previously reviewed for the treatment of OSA, but the data are quite limited, including limited population. An American Academy of Sleep Medicine (AASM) practice parameter review from 2006 did not recommend oxygen as a primary treatment for OSA. In contrast, in some cases, oxygen may be utilized as a supplement to positive airway pressure therapy in cases of refractory hypoxemia and may, in some circumstances, be an option for individuals who fail or refuse all other OSA treatments and have significant nocturnal hypoxia associated with their sleep apnea.

d. **Oral appliances.** Custom made oral appliances improve upper airway size during sleep by enlarging the upper airway and/or by decreasing upper airway collapsibility. One specific type of an oral appliance, the mandibular repositioning appliances covers the upper and lower teeth and hold the mandible in a relatively advanced position with respect to the resting position, improving the air space. Oral appliances may not be as efficacious as CPAP in treating sleep apnea, but are indicated for use in patients with mild-to-moderate OSA who do tolerate or respond to CPAP, or fail behavioral interventions to improve compliance. Oral appliances are appropriate for first line therapy in patients with primary snoring who do not respond to weight loss or positional therapy.

e. **Uvulopalatopharyngoplasty** (UPPP) is a surgical procedure in which excess soft tissue of the soft palate, uvula, and sometimes the tonsils and adenoids are removed. A recent advance in this type of approach is laser-assisted uvuloplasty. The advantages are that the laser procedure is office based and that the amount of tissue removed can be titrated to effect. However, the efficacy of these procedures in the management of sleep apnea is variable. It is estimated that these surgical approaches are effective approximately 50% of the time for amelioration of sleep apnea but are more effective for snoring. Thus patients may continue to have silent obstructive apnea after surgery.

A 2010 AASM's practice parameter on surgical treatment options for adult OSA patients reviewed the literature regarding the following specific surgical procedures: tracheostomy, maxillo-mandibular advancement, laser-assisted uvulopalatoplasty (LAUP), UPPP, tongue base submucosal radiofrequency ablation, and palatal implants.

Establishing a diagnosis of OSA and its severity by PSG prior to any surgical intervention was considered a standard recommendation by this position paper. In addition, so that patients can make an informed decision regarding therapy, the standard proposed that all patients be advised of the anticipated success rates and potential complications, related to surgical intervention as compared with the alternative treatment options for their OSA (namely CPAP and OA). If patients chose to have surgery, clinical follow-up including a nocturnal polysomnogram is a standard recommendation in order to demonstrate resolution of OSA as measures by the AHI oxygen saturation, and sleep architecture. As for the specific surgical procedure, none, with the exception of LAUP, received more than a recommendation of option as an intervention for the management of OSA. The standard recommendation was not in favor of using LAUP as a treatment for OSA. A multidisciplinary approach is recommended to identify appropriate patients for surgical interventions.

f. **Drug therapy.** When nasal CPAP is not an option, patients with mild-to-moderate OSA may benefit from drug therapy. Protriptyline at a dosage of 10 mg at bedtime with upward adjustment depending on response and side effects may be an alternative treatment. Drug therapy is generally unsatisfactory for the management of OSA. Recently, the FDA has approved the use of modafinil to improve wakefulness in patients with EDS associated with OSA if CPAP is used with adequate compliance and when total sleep time is adequate.

Recommended Readings

Allen R. Dopamine and iron in the pathophysiology of restless legs syndrome (RLS). *Sleep Med*. 2004;5:385–391.

Allen R, Becker PM, Bogan R, et al. Ropinirole decreases periodic leg movements and improves sleep parameters in patients with restless legs syndrome. *Sleep*. 2004;27:907–914.

Aurora RN, Casey KR, Kristo D, et al. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. *Sleep*. 2010;33(10):1408–1413.

Aurora RN, Zak RS, Maganti RK, et al. Best practice guide for the treatment of REM sleep behavior disorder (RBD). *J Clin Sleep Med*. 2010;6(1):85–95.

Avidan AY. Parasomnias and movement disorders of sleep. *Semin Neurol*. 2009;29(4):372–392.

Avidan AY, Kaplish N. The parasomnias: epidemiology, clinical features, and diagnostic approach. *Clin Chest Med*. 2010;31(2):353–370.

Avidan AY, Zee PC. *Handbook of Sleep Medicine*. 2nd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.

Dodson ER, Zee PC. Therapeutics for circadian rhythm sleep disorders. *Sleep Med Clin*. 2010;5(4):701–715.

Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. *Sleep Med*. 2010;11(9):807–815.

Guilleminault C, Faull KF. Sleepiness in non-narcoleptic, nonsleep apneic EDS patients: the idiopathic CNS hypersomnolence. *Sleep*. 1982;5:S175–S181.

Harsora P, Kessmann J. Nonpharmacologic management of chronic insomnia. *Am Fam Physician*. 2009;79(2):125–130.

Holty JC, Guilleminault C. Surgical options for the treatment of obstructive sleep apnea. *Med Clin North Am*. 2010;94:479–515.

The International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd ed. Westchester, IL: AASM; 2005.

Kapur V, Maganti R, Owens J, et al.; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. *Sleep*. 2007;30(11):1445–1459.

Kryger MH, Roth T, Dement WC. *Principles and Practice of Sleep Medicine*. 5th ed. Philadelphia, PA: Saunders/Elsevier; 2011.

Loube DI, Gay PC, Strohl KP, et al. Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: consensus statement. *Chest*. 1999;115:863–866.

Manthena P, Zee PC. Neurobiology of circadian rhythm sleep disorders. *Curr Neurol Neurosci Rep*. 2006;6(2):163–168.

Mignot E. Narcolepsy: pharmacology, pathophysiology and genetics. In: Kryger M, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Philadelphia, PA: Elsevier Saunders; 2005:761–779.

Mitler M, Erman M, Hajdukovic R. The treatment of excessive somnolence with stimulant drugs. *Sleep*. 1993;16:203–206.

Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report.

The National Institutes of Health Consensus Development Program. NIH State-of-the-Science Conference statement on manifestations and management of chronic insomnia in adults. *Sleep*. 2005;28:1049–1057.

Neubauer DN, Flaherty KN. Chronic insomnia. *Semin Neurol*. 2009;29(4):340–353.

Nishino S, Mignot E. Narcolepsy and cataplexy. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology*. New York, NY: Elsevier, Vol. 99. 2011:783–814.

NIH State-of-the-Science Conference Statement on manifestations and management of chronic insomnia in adults. *NIH Consens State Sci Statements*. 2005;22(2):1–30.

Overeem S, Mignot E, van Dijk JG, et al. Narcolepsy: clinical features, new pathophysiologic insights, and future perspectives. *J Clin Neurophysiol*. 2001;18(2):78–105.

Overeem S, Reading P. *Sleep Disorders in Neurology: A Practical Approach*. Chichester, West Sussex: Wiley-Blackwell; 2009.

Pack AI, Pien GW. Update on sleep and its disorders. *Annu Rev Med*. 2011;62:447–460.

Reid KJ, Zee PC. Circadian rhythm sleep disorders. *Med Clin North Am*. 2004;(3):631–651.

Reid KJ, Zee PC. Circadian rhythm sleep disorders. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology*. New York, NY: Elsevier, Vol. 99. 2011:963–977.

Riemann D, Perlis ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioral therapies. *Sleep Med Rev*. 2009;13(3):205–214.

Robinson A, Guilleminault C. Obstructive sleep apnea syndrome. In: Chokroverty S, ed. *Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects*. 2nd ed. Boston, MA: Butterworth-Heineman; 1999:331–354.

Rubins JB, Kunisaki KM. Contemporary issues in the diagnosis and treatment of obstructive sleep apnea. *Postgrad Med*. 2008;120(2):46–52.

Silber MH, Krahn LE, Morgenthaler TI. *Sleep Medicine in Clinical Practice*. 2nd ed. New York, NY: Informa Healthcare; 2010.

Wise MS, Arand DL, Arger RR, et al. Treatment of narcolepsy and other hypersomnias of central origin. *Sleep*. 2007;30(12):1712–1727.

Zee PC, Goldstein CA. Treatment of shift work disorder and jet lag. *Curr Treat Options Neurol*. 2010;12(5):396–411.

CHAPTER

56 Dizziness and Vertigo

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When investigating the source of dizziness in a patient, it is useful to organize potential etiologies into four groups. The four major causes of dizziness and vertigo are peripheral vestibular, central vestibular, medical, and unlocalized. True vertigo, particularly rotatory vertigo, is often due to a peripheral vestibular (inner ear) disorder. Presyncope and loss of consciousness are not associated with vertigo of peripheral origin and should direct the examiner to investigate other, often cardiovascular or CNS causes. These are common clinical scenarios and illustrate the varied backgrounds from which a complaint of dizziness may arise, ranging from benign annoyance to signs of potentially life-threatening events.

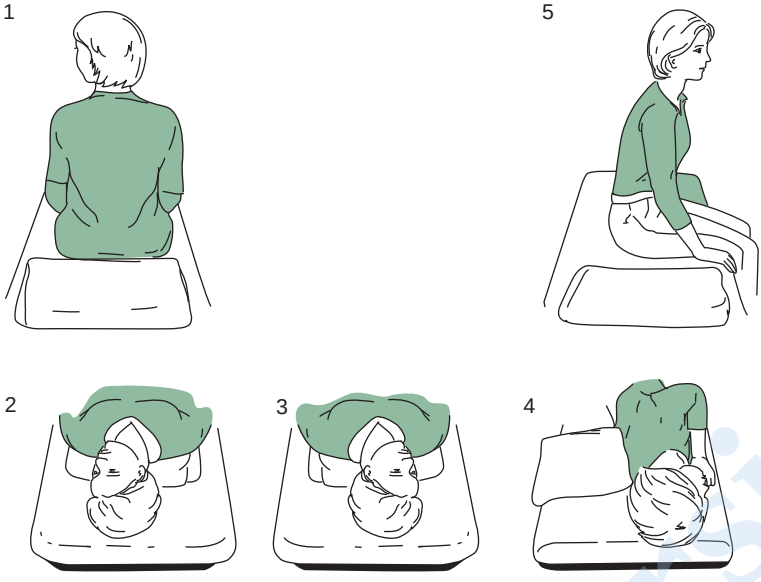
Documentation of the impact of dizziness and vertigo on a patient's quality of life is essential in formulating a treatment plan. Treatment options are driven by the severity of disease and limitation in activities of daily living. Disease impact will often differ between patients as what may be tolerable for a retired schoolteacher may not be tolerable for an airline pilot.

I. PERIPHERAL VESTIBULAR OR OTOLOGIC CAUSES OF VERTIGO

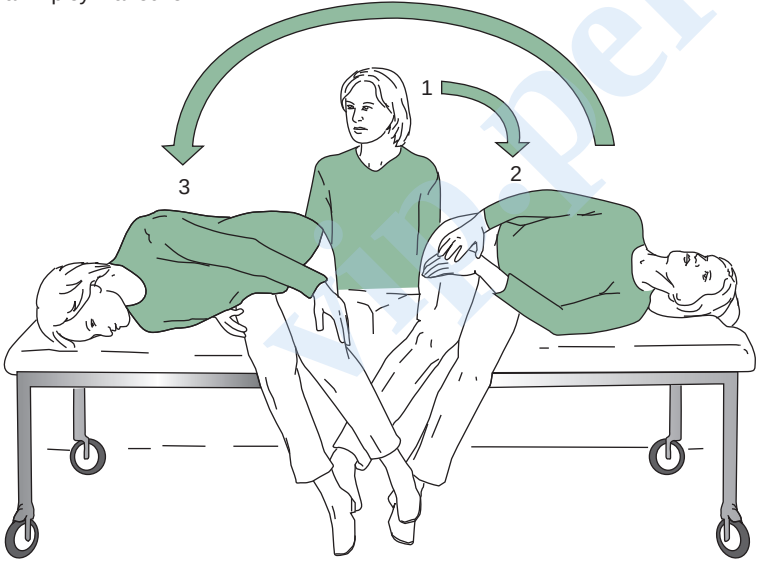
A. Benign paroxysmal positional vertigo.

1. **Clinical features.** Benign paroxysmal positional vertigo (BPPV) is characterized by brief vertigo associated with changes in head position. It is the most common cause of vertigo. It is typically the result of stimulation of the posterior semicircular canal by loose debris (calcium carbonate crystals) dislodged from the utricle. This dislodgement can result from trauma, labyrinthitis, or spontaneously. Typically the history is one of recurrent vertiginous episodes lasting not more than 1 minute and reproducible with repeated movement in the same direction. The Dix–Hallpike's test (which is illustrated in Chapter 16) is commonly employed to diagnose BPPV and identify the affected labyrinth.
2. **Treatment.** Vestibular suppressant medications can lessen vertigo intensity but do not reduce the frequency of attacks. The mainstay of treatment is repositioning exercises to move the debris from the affected semicircular canal. Both office-based repositioning techniques and home exercises may be employed to accomplish this goal. Rarely, when positional vertigo is unresponsive to repositioning maneuvers, surgery may be considered.
   a. **Epley's maneuver.** It is a common technique used for canalith repositioning. It is most effectively used when the affected semicircular canal has been identified and can therefore be targeted (see Chapter 16).
      Technique (Fig. 56.1).
      (1) With the patient sitting upright, the head is turned 45° to the offending side, and the neck is extended 45°.
      (2) From this upright position with the head turned, the patient is reclined supine with the head hung over the edge of the exam table; this position is held for 10 to 15 seconds.
      (3) The head is then slowly rotated away from the offending side, through midline, to 45° to the opposite side, keeping the neck extended throughout.
      (4) The body and head are turned to face downward opposite to the offending side.
      (5) After 10 to 15 seconds, the patient is slowly lifted to a seated upright position keeping the head turned away from the offending side.
      (6) The head is then slowly returned to midline.

b. **Modified Semont maneuver.**
Technique (described for right-sided BPPV) (Fig. 56.1).
(1) The patient sits upright on the edge of the bed with the head turned 45°to the left.
(2) The patient drops his/her head quickly to touch the right postauricular region to the bed and maintains this position for 30 seconds.



a. Epley maneuver



b. Modified Semont maneuver

FIGURE 56.1 Self-treatment of BPPV. (From Radtke A, von Brevern M, Tiel-Wilck K, et al. Self-treatment of benign paroxysmal positional vertigo: Semont maneuver vs Epley procedure. *Neurology*. 2004;63:150–152, with permission.)

(3) The patient then rolls in a swift movement toward the left side, so that the trunk is lying supine and the head comes to rest on the left side of the forehead and maintains this position for 30 seconds.
(4) The patient sits up again.

This maneuver should be performed three times daily and repeated until symptom free for 24 hours.

c. **Surgery.** Very rarely, repositioning techniques are ineffective, and in severe cases of refractory BPPV surgery may be offered. Surgical options, which can be performed by a neurotologist, include semicircular canal plugging and vestibular neuronectomy.

3. **Results.** When applied to patients with BPPV, canalith repositioning is successful in relieving symptoms in up to 90% of patients. The techniques can be performed and taught by a wide range of clinicians. In those patients with recurrent symptoms, teaching the patient repositioning techniques will allow self-treatment and continued symptomatic relief.
4. **Special circumstances.** When BPPV is bilateral, treatment begins with the side that has a more robust nystagmus on Dix–Hallpike's testing. Patients with severe disease may need pretreatment with 5 to 10 mg of diazepam 30 minutes prior to repositioning.

B. Vestibular neuronitis and labyrinthitis.

1. **Clinical features.** Vestibular neuronitis and labyrinthitis are often discussed together because of their similar presenting features. Both involve vertigo that can last for hours to days, often severe enough to induce nausea and vomiting. Labyrinthitis is associated with sensorineural hearing loss (SNHL), whereas vestibular neuronitis is not. These are typically self-limited conditions that are attributed to a viral infection. After the acute phase, vestibular equilibrium gradually returns over the course of several weeks in most patients.
2. **Treatment.** Using a combination of vestibular suppression, anti-inflammatory agents, antiemetics, and vestibular rehabilitation, treatment aims to reduce the severity and duration of acute symptomatology while allowing for vestibular recovery.
   a. **Vestibular suppression.** Vestibular suppressants are generally grouped into three categories: benzodiazepines, antihistamines, and anticholinergics (Table 56.1). Benzodiazepines work via gamma–aminobutyric acid (GABA) potentiation and subsequent inhibition of vestibular stimulation. Anticholinergics and antihistamines work to suppress vestibular input. These medications are generally well-tolerated in low doses, although it is important to realize that a high level of vestibular suppression may reduce central compensation, and thus they are best used in a limited fashion. Antiemetics are a fourth category of pharmacotherapy, often used concurrently with vestibulosuppressants to target frequently associated nausea.
      (1) **Antihistamines.** Antihistamines, notably those of the histamine-1 antagonist group, are commonly used in the management of peripheral vertigo. They are believed to exert a vestibulosuppressant effect via a central anticholinergic mechanism. Meclizine is most commonly used, starting at small doses (12.5 to 25 mg two to three times daily) and titrating to effect. Its effect is limited with adequate suppression typically lasting only 1 to 2 months. Promethazine is another antihistamine that also has antiemetic properties.
      (2) **Anticholinergics.** Scopolamine is an anticholinergic medication commonly used in the prevention of motion sickness. It is not as valuable in the management of acquired vestibulopathy, but may be effective in the prophylaxis of motion sickness.

TABLE 56.1 Common Oral Medications for Treatment of Vertigo

Medication	Class	Dose
Clonazepam	Benzodiazepine	0.25–0.5 mg q8h
Diazepam	Benzodiazepine	5–10 mg q12h
Lorazepam	Benzodiazepine	1–2 mg q8h
Dimenhydrinate	Antihistamine	50–100 mg q4h–q6h not to exceed 400 mg daily
Diphenhydramine	Antihistamine	25–50 mg q4h–q6h not to exceed 300 mg daily
Meclizine	Antihistamine	12.5–50 mg q4h–q6h
Scopolamine	Anticholinergic	0.5 mg patch q72h

(3) **Benzodiazepines.** They are a class of psychoactive drugs that work via central inhibitory GABA potentiation resulting in anxiolysis, sedation, and in some cases amnestic, anticonvulsant, and muscle relaxation effects. Lorazepam and diazepam are frequently used for their ability to prevent and mitigate attacks of dizziness and vertigo from a variety of etiologies. Diazepam at a low dose (5 to 10 mg) acts as a vestibulosuppressant and can be used for acute or chronic otologic dizziness. Care must be taken when utilizing benzodiazepines because of their increased potential for dependence and subsequent withdrawal symptoms on cessation of therapy.

(4) **Antiemetics (Table 56.2).** Antiemetics are used to relieve nausea and vomiting associated with vertigo. Prochlorperazine is a phenothiazine that exerts a strong antiemetic effect but also carries the risk of extra pyramidal side effects. Metoclopramide is a dopamine receptor antagonist and serotonin receptor antagonist/agonist with antiemetic and prokinetic properties. Ondansetron provides antiemesis via serotonin 5-HT_3 receptor antagonism.

b. **Corticosteroids/antivirals/antibiotics.** Corticosteroids may be effective in treating associated hearing loss with labyrinthitis. Although most cases of labyrinthitis are believed to arise from viral infection, the addition of antiviral therapy to corticosteroids has not been shown to offer additional benefit. Antibiotics are of value in cases of bacterial or suppurative labyrinthitis; however, the decision to use antibiotics should be dictated by objective signs of infection.

c. **Vestibular rehabilitation.** It refers to physical therapy aimed at enhancing recovery from peripheral vestibulopathy. The exercises range from simple head-turning to increasingly more complex postural and ambulation challenges with and without head movement. Simple walking is a form of vestibular rehabilitation that can be recommended to patients with limited disequilibrium. The earlier vestibular rehabilitation takes place, the better the outcome, and patients should be titrated off vestibular suppressants to optimize vestibular challenge and recovery.

3. **Results.** Although there is some support for steroid use and vestibular rehabilitation enhancing vestibular recovery, randomized control trials are lacking. Fortunately, over 90% of patients with vestibular neuronitis or labyrinthitis will return to their presymptomatic baseline.

C. Méniere's disease.

1. **Clinical features.** Méniere's disease is characterized by the constellation of fluctuating SNHL, tinnitus, and vertigo. It is often associated with "aural fullness." Episodes are recurrent and typically last 20 minutes or longer. Over time, the involved peripheral vestibular system experiences a reduction in responsiveness or "burns out." It is a disease primarily of Caucasians with a slight female bias, and onset between 40 and 60 years of age. The histopathologic correlate is endolymphatic hydrops, the result of an overaccumulation of endolymph. The pathophysiologic mechanism is believed to be the result of membranous labyrinth microruptures allowing potassium-rich endolymph to mix with potassium-poor perilymph, thus disrupting biochemical gradients and neuronal conductivity.
2. **Treatments.** Treatment of Méniere's disease is focused on vertiginous symptom control, as tinnitus and hearing loss are less amenable to intervention. Medical therapy is used at the outset of treatment with more invasive options reserved for symptoms refractory to conservative management.
   a. **Nonablative.**
      (1) **Acute.** As in labyrinthitis, antihistamines, anticholinergics, benzodiazepines, and antiemetics may be used to mitigate acute attacks of vertigo and nausea.

TABLE 56.2 Common Oral Medications for Treatment of Nausea

Medication	Dose
Metoclopramide	5–10 mg q6h
Ondansetron	8 mg t.i.d.
Prochlorperazine	5–10 mg t.i.d. to q.i.d.

Abbreviations: t.i.d., three times a day; q.i.d., four times a day.

(2) **Chronic.** Salt restriction diet and diuretics are the mainstays of medical treatment. Their efficacy is believed to result from a reduction in endolymph. A combination of hydrochlorothiazide and triamterene is a commonly used regimen and can be titrated to effect. Also limiting alcohol, caffeine, and stress may be beneficial. Those patients with poor symptom control despite these measures may then be offered nonablative options such as intratympanic steroid injection or endolymphatic sac surgery (ESS). ESS is a hearing-preserving, nonvestibular-ablative endolymphatic sac decompressive procedure. The mechanisms by which it reduces vertigo are controversial.

b. **Ablative.** For patients in whom conservative measures have failed, vestibular ablative options may be offered. Intratympanic gentamicin injection offers somewhat selective vestibular toxicity through a less invasive approach, but carries a significant risk of SNHL. Vestibular nerve section offers a high-rate of vertigo control with minimal risk to hearing. Labyrinthectomy is a complete vestibular-ablative procedure well-suited to patients with non-serviceable hearing.

3. **Results.** Diuretics have been shown to control vertigo and stabilize hearing in 50% to 70% of patients. In addition, the natural history of Ménière's disease allows for spontaneous remission of episodic vertigo in 60% to 80% of patients. For those few with refractory vertigo, intratympanic steroid and endolymphatic sac decompression is effective at controlling vertigo in approximately 80% of patients, whereas ablative procedures such as intratympanic gentamicin, vestibular neuronectomy, and labyrinthectomy control vestibular symptoms in >90% of patients.

D. Perilymphatic fistula.

1. **Clinical features.** Perilymphatic fistula is a controversial clinical entity. Theoretically, it is characterized by the abnormal communication of perilymph between the labyrinth and the middle ear via the oval window, round window, or an aberrant pathway. It may result from barotrauma, penetrating middle ear trauma, stapedectomy, or occur spontaneously. The controversy in its diagnosis centers on the difficulty in identifying a microfistula intraoperatively and the lack of clear clinical criteria. It is described most often as vertigo with extreme pressure sensitivity that may be exacerbated by Valsalva's maneuvers and pneumatic otoscopy. It may also be associated with sudden or gradual hearing loss and thus may mimic Ménière's disease.
2. **Treatments.** Small fistulae may heal spontaneously with a short course of bed rest. In situations with stable hearing or when the clinical diagnosis is questioned, a trial of vestibular rehabilitation may be attempted. When there is a clear temporal relationship between a predisposing insult (e.g., scuba diving, ear surgery, or penetrating middle ear trauma), an exploratory tympanotomy may be undertaken by a neurotologist. The surgical goal is localization of a discrete fistula and patching with autogenous connective tissue. Postoperatively, a course of bed rest is undertaken to allow healing of the graft and efforts are made to minimize Valsalva coughing and straining.
3. **Results.** Bed rest is successful in many patients, and in cases where the fistula is evident, surgery can be very effective. Consideration of an alternate diagnosis such as superior semicircular canal dehiscence syndrome may be necessary in patients who undergo negative exploration.

E. Superior canal dehiscence syndrome.

1. **Clinical features.** Superior canal dehiscence syndrome (SCDS) is a sound- and pressure-induced vertigo caused by bony dehiscence of the superior semicircular canal. The characteristic torsional vertical nystagmus occurs in the plane of the affected canal with administration of sound and pressure changes. Patient complaints are variable and include autophony, sound-induced (Tullio's phenomenon) or pressure-induced vertigo, conductive hearing loss and/or pulsatile tinnitus. Clinically, SCDS symptomatology overlaps with perilymphatic fistula and acquired horizontal canal dehiscence from cholesteatoma or chronic otitis media. However, history directs clinical suspicion and high-resolution CT demonstrating superior canal dehiscence is diagnostic.
2. **Treatments.** Surgical plugging of the affected superior canal can be beneficial in patients with debilitating symptoms due to this disorder.
3. **Results.** Success rates of surgical plugging of superior canal dehiscence are reported to range from 50% to 90%.

F. Ototoxicity.

1. **Clinical features.** Ototoxicity may be associated with a number of medications and manifests as hearing loss, tinnitus and/or dizziness, and vertigo. Clinically significant ototoxicity is commonly associated with aminoglycosides and other antibiotics, platinum-based antineoplastic agents, salicylates, quinine, and loop diuretics. Aminoglycoside gentamicin is notably vestibulotoxic, and this property is selectively utilized in vestibular ablation procedures as previously mentioned. Cessation of treatment will halt the continued insult, but recovery is variable and may be incomplete.
2. **Treatments.** Paramount to treatment is the avoidance of ototoxic medications whenever possible. Active treatment options are limited to vestibular rehabilitation and symptomatic supportive measures while central compensation and adaptation of the vestibulospinal and vestibulocervical reflexes occur.
3. **Results.** Although these compensatory mechanisms are of value, they are not typically sufficient in restoring complete function. Certainly prevention, if possible, is more effective than treatment in this condition.

G. Tumors involving the vestibulocochlear nerve.

1. **Clinical features.** Vestibular schwannoma is the most common lesion of the cerebellopontine angle (Fig. 56.2). These benign, slow-growing tumors can occupy the vestibular division of the eighth cranial nerve from the internal auditory canal to the cerebellopontine cistern. As the tumor enlarges, it can cause vestibulocochlear nerve dysfunction both from local compression as well as disruption of blood supply. Tumor progression is typically gradual allowing for contralateral vestibular and central compensation to mask vestibular loss. More commonly, unilateral hearing loss and tinnitus prompt patients to seek care. Advanced tumors may show signs of vestibulopathy and result in life-threatening hydrocephalus and brainstem compression.
2. **Treatments.** The slow-growing nature of vestibular schwannoma and the inherent surgical risks require that treatment options be tailored to each patient. Patient age and

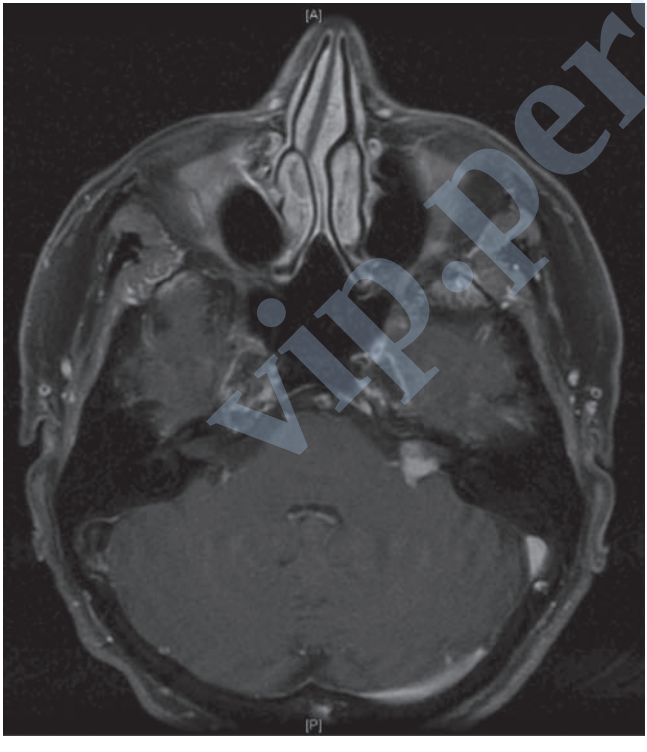


FIGURE 56.2 Left-sided vestibular schwannoma on contrast-enhanced T1-weighted axial MRI.

documentation of tumor growth must be considered in the treatment planning because a certain percentage of tumors are quiescent. Young, healthy patients with active tumor growth may be encouraged to undergo surgery. Microsurgical resection offers a chance for complete tumor resection with a low rate of recurrence. Elderly patients who are poor surgical candidates may be better suited for observation in small quiescent tumors. Radiation therapy is another treatment modality that functions to arrest tumor growth and is often reserved for patients with demonstrated tumor growth who are poor surgical candidates.

3. **Results.** Success rates in the treatment of vestibular schwannoma must be weighed against the quiescent natural history of some tumors. Radiation therapy tumor control rates are reported >95% in some series, although it is unknown what percentage of these tumors were growing. Outcomes for microsurgical control of vestibular schwannomas are comparable to radiotherapy. Hearing preservation is not always possible with surgery and is dependent on tumor size and location. In addition, long-term data on radiotherapy also shows a high-rate of progressive SNHL in spite of tumor control.

II. CENTRAL NEUROLOGIC CAUSES OF VERTIGO

A. Ischemia or infarction.

1. **Clinical features.** Disruption of vertebrobasilar circulation to the brainstem, cerebellum, and peripheral vestibular system can cause dizziness and vertigo. The hallmark of this ischemia is the association of vertigo with other focal neurologic findings, particularly in a predictable anatomic distribution. Weakness, facial paresthesia, dysarthria, ataxia, diplopia, and visual disturbances are examples of symptoms that may also be present with transient ischemia or infarction of the brainstem. Because transient ischemia may be responsible for episodic vertigo, it is important to recognize it as such to prevent potential stroke.
2. **Treatments.** General supportive measures and the use of antiplatelet and anticoagulant medications remain the cornerstones of medical therapy for the management of acute ischemic stroke. More importantly for the clinician evaluating episodic dizziness in the outpatient center is the recognition of signs of transient ischemic attacks (TIAs). Preceding TIAs are a risk factor for atherothrombotic brain infarction and should prompt evaluation of other vascular risk factors such as hypertension, diabetes, obesity, hyperlipidemia, and smoking. Additionally, cardiac evaluation may be warranted in search of possible embolic sources depending on presenting signs. Further discussion on the treatment and prevention of ischemic cerebrovascular disease is discussed elsewhere in Chapter 36.
3. **Results.** Appropriate lifestyle modifications and the addition of antithrombotic (antiplatelets or oral anticoagulants when indicated) therapy are effective in reducing the incidence of stroke and permanent deficit after stroke in at-risk individuals. No therapy is 100% effective.

B. Basilar migraine and migrainous vertigo.

1. **Clinical features.** Classically described as a condition of adolescent females, basilar migraine (see *ICHD-II*) can affect males and females of any age though it does have a female preponderance. It is characterized by an aura causing hemianopic visual changes, vertigo, ataxia, numbness, or dysarthria followed by a throbbing occipital headache often associated with nausea. Symptoms are self-limited, with the aura lasting from a few minutes to an hour and a headache of variable duration. Basilar migraine is considered a distinct clinical entity from migrainous vertigo, which is characterized by episodic vertigo, but without related neurologic symptoms and in some cases, even without headache. Because it is more difficult to diagnose without the associated symptoms, some question migrainous vertigo as a clinical entity. Diagnosis of migrainous vertigo relies on indirect evidence in the form of relationship of symptoms to migrainous triggers and response to antimigraine medications. In both cases, and particularly with vertibrobasilar migraine, there is overlap between migrainous symptoms and those of more serious cerebrovascular derangement, and a thorough evaluation should rule out other causes of vertigo before the diagnosis of migraine is applied.

2. **Treatments.** Multiple treatment regimens exist for migraine. Abortive medical therapy is directed at resolving the symptoms shortly after onset. Medications such as ergotamine and the triptans fall into this category. Patients whose symptoms are more frequent may be candidates for preventive medical therapy in the form of ß-blocking agents, tricyclic antidepressants, antiepileptic drugs (AEDs), and calcium channel blockers. The treatment of migraine is discussed elsewhere in this text.
3. **Results.** With proper selection of medical therapy, the majority of migraine patients can achieve the goal of symptom prevention.

C. Seizures.

1. **Clinical features.** Seizures do not commonly cause vertigo in isolation. They are more often associated with accompanying features of complex partial seizures such as swallowing, lip-smacking, and alteration of consciousness. They may be the result of a CNS disorder such as tumor or brain injury or result from metabolic derangement. Evaluation of new-onset seizures with or without vertigo requires a thorough history and physical examination with ancillary testing directed at identifying potential underlying causes.
2. **Treatments.** AEDs are the primary therapy for seizures. In cases refractory to medication, surgical procedures exist to remove or isolate the epileptogenic focus. These treatments are discussed in detail in Chapters 38 and 39.
3. **Results.** The goal of therapy is to eliminate symptoms strictly with medication. Predicting the likelihood of effective treatment requires analysis of the underlying cause of seizure. Brain neoplasm and structural abnormalities may be more refractory to medical therapy than metabolic derangements.

D. Multiple sclerosis (MS).

1. **Clinical features.** MS is often diagnosed in young adults. Vertigo can be an associated symptom of CNS dysfunction and may be followed some time later with isolated weakness or visual disturbance. Clinical diagnosis is confirmed with MRI and/or CSF analysis.
2. **Treatments.** There are a number of immunomodulating agents used in the treatment of MS. These and other treatments are discussed in more detail elsewhere in Chapter 40.
3. **Results.** MS is a highly variable disease, and its effects on patients are myriad. Treatments are also varied with inconsistent results. The goal of appropriate therapy is to mitigate the severity of attacks while reducing their frequency.

E. Chiari's malformations.

1. **Clinical features.** Symptoms suggestive of Chiari include headache, vertigo, ataxia, tinnitus, hearing loss, weakness, and numbness. Chiari's malformations are often associated with downbeat nystagmus in the primary position.
2. **Treatments.** Conservative measures consisting of symptomatic control may be appropriate in certain patients. Those with progressive disease may require surgical decompression of the posterior fossa.
3. **Results.** Surgical decompression often relieves or at least halts the progression of brainstem compressive symptoms.

III. MEDICAL DIZZINESS

A. Postural hypotension.

1. **Clinical features.** Postural hypotension is a classic finding in elderly patients and may result from any number of causes. Symptomatically, it is described as lightheaded or presyncopal feeling when standing from sitting or lying. It can result from diminished cardiac output, antihypertensive medication with associated vasodilation or ß-blockade, dehydration, or autonomic insufficiency from underlying diabetic neuropathy, for example.
2. **Treatments.** Most important in the treatment of postural hypotension is to recognize it as such. With this in mind, a systematic hemodynamic review must be undertaken. Modification of a current medication regimen is straightforward. Exercise and improved hydration can improve underlying cardiac decompensation, and elastic stockings may be of benefit in optimizing cardiac return.

3. **Results.** Proper identification of hemodynamic insufficiency allows treatment modifications where able and is often successful at reducing the severity and frequency of postural hypotension.

B. Arrhythmia.

1. **Clinical features.** Symptoms of cardiac arrhythmia frequently include palpitations with or without chest pain. They may be associated with presyncope or even loss of consciousness but are not typically associated with true vertigo. Diagnostic workup includes cardiac monitoring, particularly during an episode, to secure the diagnosis.
2. **Treatments.** Cardiology referral is undertaken for evaluation and management of cardiac arrhythmia. Antiarrhythmic medications, pacemakers, and radiofrequency ablation of aberrant pathways of conduction may all be considered in treatment.
3. **Results.** Appropriate treatment can be very effective in managing most cardiac arrhythmias.

C. Hypoglycemia.

1. **Clinical features.** Metabolic derangements, such as insulin-dependent diabetic hypoglycemia, may be responsible for dysequilibrium but rarely true vertigo. Episodes of hypoglycemia and dysequilibrium may present acutely in patients who have used insulin for years.
2. **Treatments.** Treatment of hypoglycemia is acutely directed at increasing the serum blood glucose level and may require tailoring the diabetic regimen to prevent future episodes.
3. **Results.** Targeted treatment along with patient education is usually successful at resolving or decreasing the frequency of symptoms.

D. Medication-associated.

1. **Clinical features.** Medications that mediate CNS effects, such as AEDs, benzodiazepines, and psychogenics, may cause primary effects and side effects that create a sensation of dysequilibrium. This dysequilibrium is distinct from postural hypotension that may arise from antihypertensive medications as described above.
2. **Treatments.** Treatment is aimed at identifying, limiting, and/or removing the offending medication. Ideally, an alternative medication is found that offers a similar therapeutic profile.
3. **Results.** Removing the offending medication will remove the associated symptoms, but as with most medications, treatment effect must be weighed against side effect profile.

E. Infection.

1. **Clinical features.** Infectious labyrinthitis occurring due to a number of viral, bacterial, and fungal agents may cause vertigo. Patient exposures, vaccination history and associated signs and symptoms help to narrow the differential diagnosis.
2. **Treatments.** Identification of the causative infectious agent allows effective treatment with antibiotics, antivirals, or other supportive measures. Administration of mumps, rubella, rubeola, and varicella-zoster vaccines is the best method to prevent viral inner ear infections. Hearing aid and cochlear implantation are audiologic rehabilitation options as well.
3. **Results.** Results of treatment largely depend on the infectious etiology.

IV. UNLOCALIZED VERTIGO

A. Psychogenic. Anxiety, depression, and personality disorder are common codiagnoses in patients complaining of dizziness. It is a bidirectional relationship in that severe organic vertigo can cause symptoms of depression and anxiety given the potential unpredictability of attacks. In addition, patients with primary psychiatric diagnoses may also identify dizziness as a complaint, described as an out-of-body experience, a sense of floating or a racing sensation. It is important not to label a patient with a psychiatric diagnosis as having psychogenic dizziness until organic causes have been ruled out. Treatment should be directed at managing both organic and psychogenic factors simultaneously. SSRI medications and other antidepressants may be valuable in that role.

B. Malingering. Unfortunately, there are patients who misrepresent their symptoms for secondary gain. Objective testing, such as posturography, can be used to identify patients who may be falsely complaining of symptoms of dizziness.

C. Postconcussive. Concussions may be the result of mild-to-moderate traumatic brain injury (TBI) resulting in transient neurologic deficit with normal CT imaging of the brain. Nausea, vomiting, headache, and dizziness may present acutely. Focal neurologic deficits typically resolve over weeks to months following mild-to-moderate TBI, but cognitive, psychological, and emotional dysfunction may persist in more severe injuries. Supportive measures and vestibular rehabilitation are utilized to speed vestibular recovery.

D. Multifactorial. Because balance is a multifactorial process maintained through visual, proprioceptive, and vestibular input, decline in one component may be masked through central compensation mechanisms. In some patients, however, particularly the elderly multiply comorbid patient, a decline in balance input may not be met with adequate central compensation and equilibrium will be difficult to reestablish. Peripheral neuropathy, poor vision, and multiple vestibulosuppressant medications are examples of factors contributing to dysequilibrium that should be addressed. Continued walking, with assistance if necessary, is often recommended in an effort to prevent further decompensation.

E. Unknown. Although thorough history, physical examination, and judicious ancillary testing are effective in identifying the cause of dizziness in most patients, there remain those few whose symptoms arise from an unidentifiable source. This can be frustrating for both clinician and patient, and requires the clinician to counsel the patient regarding reasonable expectations in achieving a mutually acceptable outcome.

Recommended Readings

Amarenco P. The spectrum of cerebellar infarctions. *Neurology.* 1991;41:973–979.

Brandt TH. Phobic postural vertigo. *Neurology.* 1996;46:1515–1519.

Chawla N, Olshaker JS. Diagnosis and management of dizziness and vertigo. *Med Clin North Am.* 2006;96:291–304.

Derebery MJ. The diagnosis and treatment of dizziness. *Med Clin North Am.* 1999;83:163–177.

Hain TC, Yacovino D. Pharmacologic treatment of persons with dizziness. *Neurol Clin.* 2005;23:831–853.

International classification of headache disorders: 2nd edition. *Cephalalgia.* 2004;24(suppl 1):9–160.

Lynn S, Pool A, Rose D, et al. Randomized trial of the canalith repositioning procedure. *Otolaryngol Head Neck Surg.* 1995;113:712–720.

Minor LB. Superior canal dehiscence syndrome. *Am J Otol.* 2000;21:9.

Radtke A, von Brevern M, Tiel-Wilck K, et al. Self-treatment of benign paroxysmal positional vertigo: Semont maneuver vs Epley procedure. *Neurology.* 2004;63:150–152.

Solomon D. Distinguishing and treating causes of central vertigo. *Otolaryngol Clin North Am.* 2000;33(3):579–601.

Troost BT. Dizziness and vertigo. In: Bradley WG, Daroff RB, Fenichel GM, et al., eds. *Neurology in Clinical Practice.* 4th ed. Boston, MA: Butterworth-Heineman; 2004: chap 18.

CHAPTER

57 Neurologic Diseases in Pregnancy

Kathleen B. Digre and Michael W. Varner

In the United States, there are 4,000,000 live births per year. It is thus common to see neurologic conditions occur in association with pregnancy. Furthermore, the physiologic changes in pregnancy can mimic neurologic diseases and can affect the severity of neurologic signs and symptoms. Not only can neurologic conditions be affected by pregnancy, but also treatment frequently must be altered to accommodate a developing fetus. Finally, pregnancy-specific conditions can present with neurologic symptoms and signs.

I. NORMAL PHYSIOLOGIC CHANGES IN PREGNANCY

A. Cardiovascular.
1. Increase of 30% to 50% in cardiac output and blood volume with singleton pregnancy (70% with twins).
2. Midpregnancy decrease in blood pressure.

B. Pulmonary.
1. Increase of 20% to 30% in minute volume.
2. Increase in respiratory rate and partially compensated respiratory alkalosis.

C. Renal.
1. Increase of 30% to 50% in renal blood flow.
2. Decreased serum level of blood urea nitrogen and creatinine (due to increased renal clearance).

D. Gastrointestinal.
1. Decreased motility.
2. Elevated alkaline phosphatase level (placental). No pregnancy-associated changes in any other liver function tests.
3. Increased cytochrome P-450 activity.

E. Hematologic.
1. Decreased hematocrit (20% to 30% increase in RBC volume but 30% to 50% increase in blood volume).
2. Increased WBC count; decreased platelet count.

F. Coagulation factors.
1. Increased levels of plasminogen, fibrinogen, and factors VII, VIII, IX, and X.
2. No change in factor V, antithrombin, or platelet adhesion.
3. Thrombophilias (e.g., antiphospholipid antibodies, protein C and S deficiency, and factor V Leiden) are more likely to produce thromboembolic complications.

G. Connective tissue. Thickening and fragmentation of reticular fibers with mild hyperplasia of smooth muscle cells.

H. Hormonal changes. Progressive increase in estrogens and progesterone until delivery.

I. Serum osmolality. Decreases from early in gestation, with resultant increase in extracellular fluid volume.

J. Neurologic. Increase in pituitary size; slight decrease in brain volume that returns to baseline postpartum.

K. Evaluating neurologic conditions in pregnancy (Table 57.1).

L. U.S. Food and Drug Administration (FDA) risk factor classification of drugs in pregnancy.
1. **Class A.** Controlled studies show no risk to fetus in the first trimester; fetal harm is remote.
2. **Class B.** No controlled studies have been completed, but there are no known risks.
3. **Class C.** Studies on animals may show effects on fetuses, but no results of controlled studies are available. The drug can be used if the risk is justified.

TABLE 57.1 Evaluating Neurologic Conditions in Pregnancy

Test	Risk to Mother	Risk to Fetus	Contraindications
MRI	None	None known	Metal, cardiac pacemaker, and otologic implant
MRI with gadolinium	None	None known	Same as above (risk category C)
CT	None	Minimal[a]	None
CT with contrast	None	Minimal[a]	Allergy to contrast medium
Angiography	Minimal in most	Minimal[a]	Allergy to contrast medium
Lumbar puncture	None	None	Incipient herniation or mass lesion
Ultrasonography	None	None	None
EEG	None	None	None
NCV/EMG	None	None	None
Tensilon test	Minimal	Minimal	Heart failure
Visual fields	None	None	None
Dilated eye examination	None	None with punctal occlusion	Incipient glaucoma
Fluorescein angiography	None	Minimal	Allergies, FDA risk category C

[a]Abdominal shielding.

Abbreviations: NCV, nerve conduction velocity.

4. **Class D.** There are risks, but the drug may be used if serious disease or life-threatening conditions exist.
5. **Class X.** Human and animal studies show risk. The risk of use outweighs any benefit.

II. SEIZURE DISORDERS IN PREGNANCY

A. Frequency. One percent of the population.

1. In an unselected population, frequency is 7 to 8 per 1,000 deliveries.
2. Antiepileptic drugs (AEDs) lower the efficacy of some oral contraceptives in some individuals making pregnancy more likely.

B. Heredity.

1. About 2% to 5% if parent has idiopathic epilepsy. Relatively higher if the parent is the mother; relatively lower if the parent is the father.
2. No significant transmission if disease is acquired.

C. Course of disease in pregnancy.

1. The best figures for disease activity during pregnancy include the following:
   a. Improved, 22%.
   b. Exacerbated, 24% (most likely to occur in the first trimester).
   c. No change, 54%.
2. Postulated mechanisms for changes in frequency during pregnancy include the following:
   a. Physiologic.
      (1) Hormonal (estrogens decrease and progestins increase seizure threshold).
      (2) Metabolic (increased cytochrome P-450 activity).
   b. Sleep deprivation.
   c. Noncompliance (e.g., fear of birth defects from taking medications).
   d. Pharmacokinetic changes in drug levels caused by: impaired absorption, increased volume of distribution, decreased albumin concentration, reduced plasma protein binding, and increased drug clearance.
   e. Folate supplementation can reduce anticonvulsant levels.
   f. Stress, anxiety.
   g. Alcohol or other drug use.
3. Seizure frequency during pregnancy does not correlate with maternal age, seizure type, drug regimen, and seizure frequency in previous pregnancies.

4. Fetal risks with generalized convulsive seizure include the following:
   a. Physical injury from maternal abdominal trauma.
   b. Hypoxic–ischemic injury due to maternal hypoxia.

D. Therapeutic options.

1. Pharmacologic.
   a. Be certain of the diagnosis.
   b. Be familiar with and use the few drugs that are the most effective for the various types of seizures.
2. **Surgery** in general should be addressed before or after pregnancy.
3. **General.**
   a. Maintain good daily habits (regularly scheduled meals, adequate sleep, and minimize stress).
   b. Avoid alcohol and sedatives.
   c. Avoid hazardous situations.
   d. Avoid ketogenic diet.

E. Drug dosages, plasma levels, and clinical management.

1. AED levels decline during pregnancy in almost all women. This does not necessarily equate with a need to increase dosage, unless seizures are not controlled.
   a. Free (non-protein-bound) drug level equates best with clinical status (seizure control and side effects) and should be obtained in pregnancies complicated by persistent or recurrent seizures or side effects.
   b. Total drug level (usual laboratory result) sufficient if the patient has good clinical control.
   c. With the exception of valproic acid, the average decline in free levels is less than that for total levels.
2. **Frequency of measurement of levels.**
   a. Ideally, preconceptional total and free levels should be obtained and optimized.
   b. Obtain non-protein-bound (free) levels every trimester (3 months), and again 4 weeks before term when: seizure types do not interfere with activities of daily living, the epilepsy is well-controlled.
   c. Obtain monthly free levels when: uncontrolled seizures interfere with activities of daily living during the year before conception, previously controlled seizures recur during pregnancy, seizures are controlled but total drug levels decrease >50% on routine screens, troublesome or disabling side effects develop, lack of compliance is suspected or confirmed.
   d. Always check levels postpartum and adjust dosage because levels often increase as the physiologic effects of pregnancy resolve within 10 to 15 days after delivery.
3. **Changing drug dosage.**
   a. Reasons not to change dosage.
      (1) Total drug levels are declining in a woman with well-controlled seizures, unless there are >30% decline in free levels and a history of poor control.
      (2) A woman taking two or more AEDs discovers that she is pregnant (the time to change to monotherapy is before conception).
   b. Reasons to change dosage.
      (1) Increased numbers of tonic–clonic seizures.
      (2) Complex partial or other seizure types that interfere with activities of daily life and the patient wants better control.
      (3) Troublesome or disabling side effects.
   c. Discontinuation of AED therapy should ideally be accomplished before conception but can be considered cautiously during pregnancy if a patient has been seizure-free for more than 2 years, has normal findings on neurologic examination, normal electroencephalographic findings, no structural brain disorder, and no history of prolonged convulsive seizures.
4. AEDs used in pregnancy (Table 57.2); breast-feeding while taking AEDs does not appear to affect cognition.
5. Other drugs to add or consider for patients with epilepsy.
   a. Folic acid.
      (1) Requirements may be further increased because of malabsorption, competitive metabolism, and increased hepatic metabolism.

TABLE 57.2 Medications Used in Epilepsy

Drug	Indication	Dosage	FDA Category	Side Effects	Breast-Feeding[a]
Phenobarbital	Generalized seizures	1–2 mg/kg/d; 90–120 mg/d	D	Sedation	Potential toxicity
Phenytoin	Generalized seizures	4–5 mg/kg/d; 300–600 mg/d	D	Gingival hyperplasia and hirsuitism	Compatible
Fosphenytoin	Status epilepticus	Maximum 100–150 mg	D	Infant risk possible PE/ min IV	Compatible
Primidone	Generalized and partial complex seizures	500–2,000 mg/d in 2 or 3 divided doses	D	Fatigue, depression, nausea; folate deficiency	Potential toxicity
Carbamazepine	Generalized, partial complex seizures	10–30 mg/kg/d divided t.i.d. or q.i.d.; maximum 1,600 mg/d	D	Diplopia, dizziness, neural tube defect headache, nausea	Compatible
Oxcarbazepine	Partial complex seizures	Initial: 600 mg/d divided b.i.d. Maintenance: 1,200 mg/d divided b.i.d.	C	Hyponatremia, rash	Probably compatible
Valproic acid	Generalized and myoclonic seizures	15–60 mg/kg/d	D	1% neural tube defect	Compatible
Valproate IV	Status epilepticus, difficult-to-control	Loading dose of 20 mg/kg in 100 ml NS over 1 hr Maintenance 15 mg/kg a day divided t.i.d.	D	Thrombocytopenia, injection site erythema	Compatible seizures
Lamotrigine	Generalized seizures Adjunctive therapy	Starting dose: 25 mg b.i.d. slow start Maximum 500 mg for partial seizures	C	Insomnia or drowsiness, rash, and nausea	Potential toxicity
Ethosuximide	Absence seizures	500–1,500 mg/d given as 1 or 2 doses	C–D	Nausea, vomiting, anorexia, agitation, and headache	Probably compatible
Felbamate	Partial onset with secondary generalization Mostly used in Lennox–Gastaut syndrome	300–400 mg t.i.d.	C	Aplastic anemia and liver failure	Potential toxicity

TABLE 57.2 *(Continued)*

Drug	Indication	Dosage	FDA Category	Side Effects	Breast-Feeding[a]
Gabapentin	Adjunctive for partial seizures	300–600 mg t.i.d.	C	Fatigue	Probably compatible
Tiagabine	Partial and tonic–clonic seizures	30–50 mg/d divided doses	C	Dizziness and sedation	Probably compatible
Topiramate	Adjunctive, partial, and tonic–clonic seizures	12.5–25 mg/d with gradual increase to 6 mg/kg or 400 mg/d	D	Mental dullness, renal calculi; cleft palate	Potential toxicity
Zonisamide	Partial, generalized, or myoclonic seizures	Initial: 100–200 mg/d	C	Hypersensitivity reaction and nephrolithiasis	Potential toxicity
		Maintenance: 400–800 mg/d divided b.i.d.			Probably compatible
Levetiracetam	Partial or generalized seizures	Initial: 1,000 mg/d divided b.i.d.	C	Fatigue and weakness	Probably compatible
		Maintenance: 1,000–3,000 mg/d divided b.i.d.			
Trimethadione	Abscence Seizures	300-600 mg qid-tid (adult dosage)	X first trimester; D thereafter	Rash, sore throat, fever, drowsiness, fatigue, sunlight sensitivity	Probably Compatible
Vigabratin	Adjunctive in treatment resistant epilepsy, and refractory complex partial seizures	500 mg bid	C (D in Australia)	Watch vision; restricted use due to retinal toxicity	Possibly Compatible
Lacosamide	Adjunctive in treatment of partial seizures	50 mg bid (Max dose 400 mg daily)	C	Blurred vision, imbalance, mood or behavioral changes, suicidal thoughts, syncope	Unknown

[a]Watch how infant does.

Abbreviations: IM, intramuscular; t.i.d., three times a day; q.i.d., four times a day; b.i.d., twice a day; NS, normal saline solution.

See text: Source: Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation.* 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005.

(2) Increased supplementation may precipitate seizures by lowering anticonvulsant levels.
(3) Best advice is to maintain usual supplementation.
(4) Compelling evidence links the folic acid antagonism properties of AEDs to relatively increased risk of fetal neural tube defects in women taking anticonvulsants during the first trimester (neural tube defects form, or do not form, 26 to 28 days after conception). *Women of reproductive potential should take continuous folic acid supplementation (400 mg per day) whether or not they are considering pregnancy.*

b. Vitamin K should be administered (10 mg by mouth daily) to all pregnant women receiving AEDs beginning 4 weeks before expected delivery until birth to minimize the risk of neonatal hemorrhage. If a woman has not received vitamin K before delivery, consideration should be given to parenteral vitamin K administration.
c. Vitamin D not routinely supplemented.

6. Birth defects in infants of epileptic mothers.
a. Should be discussed with all epileptic women of reproductive age, irrespective of whether or not they are planning pregnancy (50% of pregnancies are unplanned).
b. Other factors that may explain the increased incidence of anomalies in infants of epileptic mothers are as follows:
(1) Increased incidence of anomalies in infants of epileptic mothers not taking AEDs. The only anomalies that are more common in phenytoin-exposed fetuses are hypertelorism and digital hypoplasia.
(2) Increased incidence of characteristic malformations in infants of epileptic fathers, described as being intermediate between treated and untreated epileptic mothers.
(3) A specific metabolic defect (epoxide hydrolase deficiency) more common in persons with epilepsy may predispose to damage in some cases. Autosomal codominant and increased fetal anomalies.
(4) Epilepsy may represent an underlying genetic disease.
(5) The defects may result from an AED-mediated relative folate deficiency. (Folate antagonists are known abortifacients and teratogens; see discussion above.)

7. AED teratogenesis should be discussed with all epileptic women of reproductive age.
a. Fetal anticonvulsant syndrome occurs in 3% to 5% of epileptic women and can occur in association with use of any anticonvulsant medication. The relative risk is dose dependent. This syndrome is being seen with decreasing frequency as fewer women receive polytherapy and more receive monotherapy.
(1) Craniofacial (cleft lip and palate) and digital dysmorphic changes.
(2) Growth deficiency.
(3) Microcephaly.
(4) Cardiac defects.
(5) Mental retardation.
b. AEDs and neural tube defects.
(1) Risk is 1% to 2% for valproic acid and slightly less for carbamazepine. It is <1% for other anticonvulsants. However, these risks are >0.1% population-wide risk in the United States.
(2) The relative risk is dose related.
(3) If the medications are necessary for seizure control, the patient should be offered maternal serum α-fetoprotein and ultrasound screening.
c. Trimethadione is clearly teratogenic and is contraindicated in pregnancy.

8. Breast-feeding.
a. Most AEDs cross into breast milk, although at low levels; the higher the protein binding of the AED, the less that is passed into breast milk. Recent studies show no cognitive change in babies breast fed while mother takes AED.
b. **Contraindications** to breast-feeding include poorly controlled maternal seizures, rapid somnolence on the part of an initially hungry infant, which suggests a drug effect.

F. Onset of seizures during pregnancy: differential diagnosis.

1. Rule out eclampsia. The most common multisystem disease in late pregnancy is preeclampsia or eclampsia.

2. **Cortical venous thrombosis,** especially late in pregnancy and in the immediate puerperium.
3. **Tumors** are especially likely to manifest in the first trimester, because this is when the pregnancy-associated increase in extracellular fluid begins. Meningioma tends to expand during pregnancy (response to the progressive increases in estrogen and progesterone).
4. **Intracranial hemorrhage.**
5. **Gestational epilepsy is** a diagnosis of exclusion and represents only a small fraction of all women who have initial seizures while pregnant.

G. **Status epilepticus** during pregnancy (follow guidelines for non-pregnant patients).

1. Less than 1% of all pregnant epileptic women.
2. Not an indication for termination of pregnancy.
3. Management should follow standard treatment of status epilepticus. Hospitalize, securing the airway, intravenous (IV) access for normal saline solution and B vitamins, baseline laboratory studies including electrolytes, CBC, glucose, calcium, and arterial blood gases. Maternal and fetal vital signs, including ECG and fetal heart rate monitoring. In addition administer the following:
   a. Glucose bolus (50 ml of D50).
   b. Thiamine (100 mg intramuscularly or intravenously).
   c. Begin lorazepam (0.1 mg per kg IV, not to exceed 2 mg per minute) or diazepam (5 to 15 mg IV in 5 mg boluses) and fosphenytoin (150 mg per minute) or phenytoin 18 to 20 mg per kg IV, not to exceed 50 mg per minute, with ECG and blood pressure monitoring, administered in nonglucose-containing fluids).
   d. If seizures persist, intubate and begin either phenobarbital (20 to 25 mg per kg IV, not to exceed 100 mg per minute). Alternatives include midazolam, propofol, levtriacetam, or IV valproic acid (if absolutely necessary).
   e. If seizures still persist, institute general anesthesia with halothane and neuromuscular junction blockade. (See Chapters 38 and 39.)

III. HEADACHE

A. The most common headache diagnoses are as follows:

1. **Migraine** (with or without aura) occurs in 10% to 20% of women of childbearing age. Unilateral or bilateral throbbing headaches associated with photophobia, phonophobia, nausea, or vomiting may be exacerbated by activity.
2. **Tension-type headache** is very common. Mild-moderate headache, without nausea and vomiting, may be relieved by activity.

B. **Genetics of migraine.** Migraine is more common in affected families. Hemiplegic migraine is autosomal dominant associated with calcium channel genes located on chromosomes 1 and 19.

C. **Course of migraine in pregnancy.**

1. The condition of most women with migraine improves when they are pregnant. This is especially true with menstrual migraine and migraine whose onset was at menarche.
2. About 10% to 20% of headaches worsen or have the initial onset during pregnancy, usually in the first trimester. Many of these may be migraine aura without headache.
3. Migraineurs have no increased risk of complications during pregnancy, but headaches usually recur near term and in the puerperium.
4. Multiparous migraineurs may have an increase in headaches in the third trimester, whereas nulliparous women report less headache activity in pregnancy and the puerperium.

D. The **differential diagnosis** of headache or migraine occurring for the first time in pregnancy includes the following:

1. Severe preeclampsia—headache with hypertension should bring this diagnosis to the forefront.
2. Cerebral venous thrombosis.
3. Stroke (carotid or vertebral artery dissection).
4. Intracranial hypertension (increased intracranial pressure [ICP]).
5. Intracranial hemorrhage.
6. Brain tumor.

E. Therapeutic options.

1. Nonmedication treatment.
   a. Adequate sleep.
   b. Avoidance of dietary and environmental trigger factors.
   c. Biofeedback, relaxation therapy, massage, physical therapy, and heat or ice packs.
2. **Acute medication treatment principles.**
   a. Prevention of nausea (Table 57.3).
   b. Management of pain (Table 57.4).
   c. Sedation (Table 57.5).
3. **Prophylactic treatment.** In general, avoid daily medications, but if headaches are too severe or interfere excessively with life, daily treatment may be needed. In general, monotherapy should be attempted. The lowest dosage should be encouraged (Table 57.6).

TABLE 57.3 Acute Migraine Treatment in Pregnancy: Nausea Prevention

Drug	Dosage (mg)	FDA Schedule	Side Effects	Breast-Feeding[a]
Promethazine	25–75 p.o., p.r., IM	C: trimester 1	—	Probably compatible
		B: trimester 2, 3	—	
Hydroxyzine	25–75 p.o., IM	C	Fatigue	Probably compatible
Prochlorperazine	10–25 p.o., p.r., IM, IV	C	Dystonic reaction	Potential toxicity
Trimethobenzamide	200–250 p.o., p.r.	C	—	Potential toxicity
Chlorpromazine	25 p.o., p.r., IM, IV	C	Dystonic reaction	Potential toxicity
Metoclopramide	5–10 IM, IV	B	Dystonic reaction	Probably compatible
Ondansetron	4 p.o., IV	B		Probably compatible

[a]Watch how infant does.

Abbreviations: p.o., orally; p.r., rectally.

Source for classification, Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005.

TABLE 57.4 Acute Migraine Treatment in Pregnancy: Pain Treatment

Drug	Dosage (mg)	FDA Schedule	Side Effects	Breast-Feeding
Acetaminophen	350–500	B	—	Compatible
Aspirin	325–650	C	Bleeding, diathesis, in utero closure of ductus arteriosus, oligohydramnios: Risk first & third trimesters	Potential toxicity
Caffeine		B	—	Potential toxicity
Butalbital-compounds		C	Possible neonatal withdrawal with heavy use	Potential toxicity
Isometheptene	Two at onset, then 1 per hour to max 5 per 24 hr	C		Probably compatible
NSAIDs[a]				
Ibuprofen	200–800	B	Bleeding diathesis, oligohydramnios, in utero closure of ductus arteriosus	Compatible

TABLE 57.4 *(Continued)*

Drug	Dosage (mg)	FDA Schedule	Side Effects	Breast-Feeding
Naproxen	200–500	B	Bleeding diathesis, oligohydramnios, closure of ductus arteriosus	Probably compatible
Ketorolac	Oral/IV	C		Probably compatible
Triptans				
Sumatriptan	25–100 p.o. 20 n.s. 4–6 s.c.	C	Contraindicated in coronary artery disease	Probably compatible
Zolmitriptan	2.5–5 p.o.	C	Contraindicated in coronary artery disease	Probably compatible
Naratriptan	1.25–2.5 p.o.	C	Contraindicated in coronary artery disease	Probably compatible
Rizatriptan	10 p.o.	C	Contraindicated in coronary artery disease	Probably compatible
Eletriptan	20–40	C	Contraindicated in coronary artery disease	Probably compatible
Almotriptan	12.5	C	Contraindicated in coronary artery disease	Probably compatible
Frovatriptan	2.5	C	Contraindicated in coronary artery disease	Probably compatible
Narcotic (use with antiemetic)				
Butorphanol	—	C	Respiratory depression, nausea	Probably compatible
Meperidine	50–100	B	Respiratory depression, nausea	Compatible
Ergotamine	Avoid	X	Possible abortifacient	Contraindicated

[a]NSAIDs, nonsteroidal anti-inflammatory drugs. Use in pregnancy should be restricted to <48 hr (>48 hr of consecutive therapy is associated with progressive risk of in utero closure of the ductus arteriosis, renal damage, and platelet dysfunction).
Abbreviations: n.s., nasal spray; s.c., subcutaneously.
Source for FDA rating: Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005.

TABLE 57.5 Acute Migraine Treatment in Pregnancy: Sedation

Drug	Dose	FDA Schedule	Side Effects	Breast-Feeding[a]
Chloral hydrate	500–1,500	C	—	Probably compatible
Pentobarbital	—	D	Withdrawal	Potential toxicity
Hydroxyzine	25–75	C	—	Probably compatible
Meperidine (plus antiemetic)		B	—	Probably compatible
Diazepam	5–10	D	Lethargy	Potential toxicity
Lorazepam	—	D		Potential toxicity
Clonazepam	0.5–1.0	C–D	—	Potential toxicity
Chlorpromazine	25–50	C	Dystonic reaction; decreased pressure	Potential toxicity

[a]Watch infant.
Source: Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005.

TABLE 57.6 Migraine Prophylaxis in Pregnancy

Drug	Dosage	FDA Schedule	Side Effects	Breast-Feeding[a]
ß-Blockers				
Propranolol	20–80	C	Possible IUGR,[b] hypotension prematurity	Compatible
Nadolol	10–40	C	Possible IUGR	Compatible
Timolol	10–30	C	Possible IUGR	Compatible
Tricyclic antidepressants				
Amitriptyline in pregnancy	10–75	C	Limb deformities	Potential toxicity
Nortriptyline	10–75	C	—	Potential toxicity
Imipramine	10–75	D	—	Potential toxicity
Desipramine	10–75	C	—	Potential toxicity
Cyproheptadine	4 mg	B	Weight gain	Probably compatible
Calcium channel blockers				
Verapamil	80–240	C	Constipation	Probably compatible
Nifedipine	10–30	C	Decreased blood pressure	Probably compatible
Amlodipine	2.5–5	C	—	Probably compatible
Anticonvulsant				
Gabapentin	100–300	C	Fatigue	Probably compatible
Topiramate	50–100 mg	D	Acidosis, weight loss; cleft palate	Potential toxicity
Valproate	500–1,000 mg	D	Weight gain, hair loss Neural tube defects	Potential toxicity

[a]Watch infant.
[b]Contraindicated drugs: methysergide, valproic acid.
Abbreviation: IUGR, intrauterine growth retardation.

IV. TUMORS

A. Incidence.
1. Probably 100 per year nationwide.
2. Pregnancy does not increase the risk of brain tumors but does increase the likelihood of symptoms.
3. The types of tumors are identical to those observed in nonpregnant women of the same age, primarily glioma (32%), meningioma (29%), acoustic neuroma (15%), and others (24%).

B. Clinical features include headache, nausea and vomiting, papilledema, focal deficits, or seizures.

C. Diagnosis is made by imaging: MRI with contrast enhancement (gadolinium) or CT with contrast enhancement (Table 57.1).

D. Treatment.
1. Dexamethasone (risk factor C).
   a. Dosage: 6 mg every 6 hours or 4 mg every 4 hours.
   b. Problems: gastrointestinal; Cushingoid changes with prolonged use.
2. Mannitol (risk factor C) for acute brain swelling.

E. Pituitary tumors.
1. **Course of disease.**
   a. **Microadenoma** rarely is symptomatic (5%).
   b. **Macroadenoma** is symptomatic in 15% to 35% of cases.

2. **Visual field** evaluation must be performed for macroadenoma.
3. **Treatment.**
   a. Bromocriptine (risk factor B) may be taken throughout pregnancy if the tumor enlarges. (Caution is advised in breast-feeding.)
   b. If vision is threatened, surgical treatment is appropriate.
4. **Sheehan's syndrome** is pituitary infarction, frequently associated with tumor or placental abruption.
   a. Manifests as inability to lactate, hypopituitarism, and hypothyroidism.
   b. Treatment involves steroid and thyroid replacement.
5. **Lymphocytic hypophysitis** mimics pituitary adenoma and suprasellar masses because it manifests as endocrinologic abnormalities, headaches, and a suprasellar mass at imaging. Lymphocytic hypophysitis occurs in pregnant and postpartum women. Biopsy often is needed to make the diagnosis. Steroid treatment with dexamethasone (category C) often is helpful.

V. PSEUDOTUMOR CEREBRI

Pseudotumor cerebri (idiopathic intracranial hypertension) is characterized by increased ICP not caused by an intracranial space-occupying lesion demonstrated at MRI or CT. Pregnancy does not cause pseudotumor cerebri. However, this disorder can occur in association with pregnancy. Pregnancy does not by itself cause visual loss. Pseudotumor cerebri does not cause miscarriage.

A. Symptoms and signs. Headache is the most common symptom (>90% of cases). Patients are otherwise alert and healthy. There are visual symptoms (transient visual obscurations) and auditory symptoms (whooshing noises). Signs include papilledema in almost all cases, cranial nerve VI palsy. Most women are obese.

B. Differential diagnosis of papilledema and no mass lesion in pregnancy.

1. Cerebral venous thrombosis (most important; most frequently needs to be excluded).
2. Venous hypertension.
3. Meningitis.
4. Syphilis.

C. Evaluation must include an imaging procedure (MRI and MR venography), CSF with opening pressure, and CSF constituents. Because the greatest threat to the patient is visual loss, visual acuity and visual field examinations must be performed frequently.

D. Treatment options.

1. **Medical treatment.**
   a. Weight loss (restriction of weight gain is better than substantial weight loss).
   b. Frequent lumbar puncture.
      (1) Safe.
      (2) Painful, often difficult.
   c. Acetazolamide (500 to 2,000 mg) (risk C); compatible with breast-feeding.
   d. Furosemide (Lasix; Aventis, Bridgewater, NJ, USA) (risk C).
   e. Chlorthalidone (risk B); compatible with breast-feeding.
2. **Surgical treatment.**
   a. Optic nerve sheath decompression is the preferred procedure to save vision.
   b. Lumbar and ventriculo-peritoneal shunts can be difficult for pregnant patients due to displacement/compression from the enlarging uterus.

VI. CEREBROVASCULAR DISEASE

A. Attributable risk of ischemic stroke or intracerebral hemorrhage in pregnancy or the puerperium is 8.1/100,000 pregnancies. The causes of stroke during pregnancy are listed in Table 57.7.

1. Arterial stroke manifests as paresis but without altered consciousness or seizures; represents 90% of strokes *during pregnancy*.
2. **Venous stroke** manifests as headache, seizures, increased ICP, and alteration of consciousness; represents 80% of strokes *during puerperium*.

TABLE 57.7 Causes of Stroke in Pregnancy

- Arterial occlusive disease
- Thrombotic cause
  - Atherosclerotic
  - Cervicocephalic FMD
  - Cervicocephalic arterial dissections
- Embolic source
  - Cardiac
    - Peripartum cardiomyopathy
    - Mitral valve prolapse
    - Rheumatic heart disease
    - Endocarditis (infective and nonbacterial)
    - Paradoxical embolism
    - Atrial fibrillation
    - Amniotic or air embolism
- Venous occlusive disease
  - Hypercoagulable state (antithrombin, protein S or protein C deficiencies, factor V Leiden deficiency, hyperhomocysteinemia)
  - Infection
- Drugs that can induce stroke:
  - Illicit drugs: cocaine, methamphetamine
  - Other drugs: sympathomimetics: phenylpropanolamine; ergotamine, bromocriptine, isometheptene
- Hypotensive disorders
  - Watershed infarction
  - Sheehan's pituitary necrosis
- Hematologic disorders
  - Lupus anticoagulant, Sneddon's syndrome
  - Thrombotic thrombocytopenic purpura
  - Sickle cell disease
  - Antithrombin deficiency, protein C and protein S deficiencies
  - Hyperhomocysteinemia
  - Factor V Leiden deficiency
  - Prothrombin G20210A mutation
  - MTHFR deficiency
- Arteritis and angiopathy
  - SLE
  - Infectious arteritis (syphilis, tuberculosis, meningococcal)
  - Cerebral angiitis
  - Takayasu's arteritis
  - Postpartum cerebral angiopathy
  - Cervicocephalic FMD and dissections
- Intracerebral hemorrhage
  - Eclampsia and hypertensive disorders
  - Cerebral venous thrombosis
  - Choriocarcinoma
  - AVMs
  - Vasculitis
  - Infective endocarditis
  - Moyamoya disease
  - Tumors (primary and metastatic)
- SAH
  - Aneurysm (saccular, mycotic, traumatic, etc.)
  - AVM (cerebral, spinal cord, and angiomas)
  - Eclampsia
  - Vasculitis

TABLE 57.7 *(Continued)*

Choriocarcinoma
Cerebral venous thrombosis
Others
Carotid cavernous fistula
Dural vascular malformation
Carotid and vertebrobasilar arterial dissection (cervicocephalic FMD)

Abbreviations: FMD, fibromuscular dysplasia; SLE, systemic lupus erythematosus; AVM, arteriovenous malformations.

Modified from Digre KB, Varner MW. Diagnosis and treatment of cerebrovascular disorders in pregnancy. In: Adams HP, ed. *Handbook of Cerebrovascular Diseases.* New York, NY: Marcel Dekker; 2005:805–850.

3. **Intracranial hemorrhage** characteristically manifests as sudden onset of headache, loss of consciousness, and accompanying signs of neck stiffness and altered blood pressure.
4. **Diagnosis.**
   a. CT and MRI (newer techniques of diffusion and perfusion may show early injury).
   b. Angiography occasionally required.
   c. Cardiac evaluation (transesophageal echocardiography—look also for right to left shunt).
   d. Appropriate laboratory studies. The factor V Leiden mutation is now thought to be associated with at least one half of all cases of venous thromboses among white women. Consider protein C or protein S deficiency (may be falsely depressed simply because of pregnancy), antithrombin, antiphospholipid antibodies, platelets, fibrinogen, and homocysteine levels.
5. Treatment is directed at the underlying cause; treatment should be individualized.
   a. **Heparin,** unfractionated or low-molecular weight, does not cross the placenta and can therefore be used safely during pregnancy. Low-molecular weight heparin (risk category B) has been used. Safe for breast-feeding.
   b. **Warfarin** (risk category D; X in first trimester; compatible with breast-feeding) crosses the placenta and is contraindicated during pregnancy due to the embryopathy associated with use.
   c. **Low-dose aspirin** (81 mg per day) (risk category C) can be used safely in pregnancy when clinically indicated. Other antithrombotic agents could be considered: Clopidrogel (risk category B) is an alternative to aspirin.
   d. Management of acute ischemic stroke with tissue plasminogen activator (e.g., Alteplase [FDA C]; Urokinase [FDA B]) is not currently recommended although there are isolated case reports of benefit.
   e. Manage elevation of homocysteine levels with folate.

B. Cerebral venous thrombosis.

1. Occurs primarily postpartum. The signs and symptoms include headache, seizures, hemiplegia, papilledema, and fluctuating obtundation and/or coma, especially in internal cerebral vein thrombosis.
2. **Diagnosis** optimally with MRI and MR venography; angiography, or venography occasionally is needed.
3. **Treatment.**
   a. Correction of predisposing factors (infection and dehydration).
   b. Control of seizures.
   c. Use of antiedema agents when appropriate.
   d. Anticoagulation (see sections **VI.A.5.a.** through **c.**).
4. **Risk factors for cerebral venous thrombosis include** cesarean delivery, hypertension, infection other than pneumonia or influenza, drug abuse, especially cocaine, methamphetamines, and IV drug abuse.

C. Postpartum cerebral angiopathy is a rare cause of a stroke-like syndrome characterized by seizure and focal neurologic deficits. Reversible cerebral vasoconstriction is found at

angiography. Medications such as ergot alkaloids (e.g., ergonovine, bromocriptine, and ergotamine) and certain vasoconstrictive agents (isometheptene and sympathomimetic drugs) have been reported to cause the disorder. Treatment has been mainly supportive.

D. Hematologic disorders often manifest more frequently in pregnancy.

1. Antiphospholipid antibody syndrome is associated with recurrent pregnancy loss, fetal growth restriction, and severe preeclampsia and eclampsia.
2. Sickle cell disease.
3. Deficiencies of antithrombin, or protein C or S.
4. Thrombophilia, especially factor V Leiden mutation.

E. Subarachnoid hemorrhage (SAH). Causes include:

1. Intracranial aneurysm.
   a. Thought to be present in 1% of all women of reproductive age; more likely in older, parous women.
   b. A significant contributor to maternal mortality.
   c. Rupture probably equally likely throughout pregnancy.
   d. Diagnosis requires CT, lumbar puncture to look for RBCs, and angiography.
   e. Optimum outcomes with surgical correction.
   f. Avoid nitroprusside because of its cyanide effect on the fetus. Hypertension can be controlled with verapamil or nimodipine.
   g. Vaginal delivery should be anticipated after successful clipping unless obstetric contraindications exist. If delivery occurs before clipping, cesarean section or forceps delivery with epidural anesthesia is indicated.
   h. Vasospasm can be managed with nimodipine (FDA C). Volume expansion must be monitored, because pregnant women are relatively more prone to pulmonary edema (decreased osmotic pressure).
   i. Outcome.
      (1) Grades 1 through 3: with expedited surgery, 95% successful outcome expected.
      (2) Grade 4: 45% to 75% mortality.
      (3) Fetal outcome: 27% mortality rate without surgery.
   j. Subsequent pregnancies after successful clipping have a good prognosis.
   k. **Asymptomatic aneurysm** should be treated if >7 mm in diameter.
2. **AVM.**
   a. Characteristically occurs in younger women who have had fewer pregnancies.
   b. Diagnosis requires CT, lumbar puncture, and angiography.
   c. The aneurysm should be corrected, if possible, surgically or with embolic therapy.
   d. Stereotactic radiation therapy is not indicated during pregnancy.
   e. Delivery is vaginal with epidural anesthesia and low-outlet forceps.

F. Eclampsia, severe preeclampsia.

1. **Definition.**
   a. Preeclampsia (new onset hypertension and proteinuria beyond 20 weeks gestation) complicates 5% to 7% of pregnancies.
   b. **Severe preeclampsia.** One or more of the following is present: persistent blood pressure 160 per 110 mm Hg, 5 g proteinuria in 24 hours, oliguria (500 ml per 24 hours), elevated results of liver function tests, thrombocytopenia, persistent visual disturbances or headache, epigastric pain, pulmonary edema, fetal growth restriction not explainable by other causes.
   c. **Eclampsia.** Seizures or coma in a woman with preeclampsia in whom no other explanation can be found.
   d. **HELLP syndrome.** A form of severe preeclampsia characterized by *h*emolysis, *e*levated results of *l*iver function tests, and *l*ow *p*latelet counts.
2. **Symptoms and physical findings.**
   a. Headache, dizziness, scotomata, nausea, vomiting, and abdominal pain.
   b. Generalized edema.
   c. Funduscopic findings: segmental vasospasm, serous retinal detachment.
   d. Neurologic finding: hyperreflexia; cortical blindness.
   e. Bedside testing: visual acuity, Amsler's grid for detection of scotomata.

3. **CT and MRI findings.**
   a. **CT.** Edema and hypodense lesions 75%, hemorrhage 9%.
   b. **MRI.**
      (1) **Severe preeclampsia.** Deep white-matter signals on T2-weighted images
      (2) **Eclampsia.** Signals on T2-weighted images at gray matter–white matter junctions, particularly in the parietal–occipital areas; cortical edema, hemorrhage; looks very much like hypertensive encephalopathy or posterior reversible encephalopathy.
4. **Treatment.**
   a. Delivery.
   b. Magnesium sulfate (FDA B; compatible with breast-feeding) is superior to IV diazepam and phenytoin in randomized controlled trials.
      (1) Administered in a 4 to 6 g loading dose followed by 2 g per hour intravenously.
      (2) Side effects include weakness, diplopia, ptosis, blurred vision, nausea, vomiting, and respiratory depression. *Use with caution in the care of patients with reduced renal clearance or neuromuscular diseases such as myasthenia gravis.*
      (3) Neurologic findings of magnesium toxicity include diminished muscle stretch reflexes, ptosis and diminished accommodation, nausea, flushing, and respiratory depression.
   c. Decrease blood pressure when necessary with an antihypertensive medication such as hydralazine or labetalol. Blood pressure needs to be controlled to minimize risk of maternal vascular accidents (usually below 160 per 110 mm Hg) but kept high enough to adequately perfuse mother and fetus.
   d. Control seizures with an AED such as diphenylhydantoin (fosphenytoin) only if $MgSO_4$ is unsuccessful.
   e. Manage cerebral edema or herniation with hyperventilation, steroids, or mannitol after delivery.
6. **Postpartum eclampsia** (one-third of eclamptic convulsions do not begin until after delivery, usually within 24 to 48 hours after delivery), usually defined as within 7 days of delivery. Late postpartum eclampsia can occur up to 10 to 14 days after delivery. Consider the possibility of stroke, venous thrombosis, or reversible angiopathy if late postpartum eclampsia is being considered.
7. **Outcome.**
   a. The maternal mortality rate in the United States is 1% to 2%.
   b. The perinatal mortality rate is 13% to 30%.
8. **Complications.**
   a. Intracranial hemorrhage, frequently from uncontrolled hypertension.
   b. Congestive heart failure, frequently from iatrogenic fluid overload.
   c. Intrahepatic hemorrhage.

VII. MULTIPLE SCLEROSIS

A. Multiple sclerosis (MS) does not affect pregnancy per se, or vice versa. Although recent studies do show that there may be increased relapses postpartum, especially in the first 6 months postpartum (particularly in the relapsing-remitting form), pregnancy does not affect the rate of disability.
1. Patients who have sphincter disturbances or paraplegia may experience increased difficulty during pregnancy.
2. There is no evidence of vertical transmission of MS.
3. MS does not occur more frequently in pregnancy.

B. Management of acute MS in pregnancy (Table 57.8).
1. Steroids (see Chapter 40).
2. The interferons and copolymer are not yet recommended in pregnancy, although patients who were pregnant have used the medications without fetal harm.

TABLE 57.8 Drugs Used in the Management of MS

Drug	Use in MS	FDA Schedule	Side Effects	Breast-Feeding
IV Methylprednisolone	Acute exacerbations	C	Anxiety, gastrointestinal distress	Compatible
Interferon ß-1a (Avonex)	Prevention of exacerbations (relapsing–remitting)	C	Fatigue, malaise, low fever	Probably compatible
Interferon ß-1b (Betaseron)	Prevention of exacerbations (relapsing–remitting)	C	Fatigue, malaise	Probably compatible
Glatinamer acetate (Copaxone)	Prevention of exacerbations (relapsing–remitting)	B	Fatigue	Probably compatible
Methotrexate	Chronic progressive	X, do not use	—	Contraindicated
Azathioprine	Chronic progressive	D	—	Potential toxicity
Mitoxantrone		D	Cardiac	Avoid
Natalizumab		C	Spontaneous Abortions reported	Avoid
Fingolmod (Gilyena)	Relapsing-remitting	C	leukopenia	Unknown
Intravenous immunoglobulin	Optic-spinal variants	C		Probably safe
Symptomatic management of MS comorbidities				
Baclofen	Spasticity	B	—	Probably compatible
Amantadine	Fatigue	C	—	Potential toxicity
Modafinil (Provigil)	Fatigue	C		Potential toxicity

VIII. ROOT LESIONS AND PERIPHERAL NEUROPATHY

A. Lumbar disk.

1. Signs and symptoms are the same as in nonpregnant patients.
2. Generally treated nonoperatively. Consider surgery if there are bilateral symptoms or disturbance of sphincter function. Surgery frequently associated with increased blood loss due to increased collateral flow.

B. Carpal tunnel syndrome.

1. Often exacerbated during pregnancy due to increase in extracellular fluid.
2. Pain and paresthesia commonly are worse at night and tend to be worse in the dominant hand.
3. Symptoms usually respond to nocturnal wrist splinting and resolve within 3 months postpartum.

C. Bell's palsy.

1. Facial paresis of lower-motor neuron type when no other specific etiologic agent can be found. Signs and symptoms include abrupt onset, often with pain around the ear; feeling of facial stiffness and pulling to one side; difficulty closing the eye on the affected side; taste disturbances; and hyperacusis.
2. Approximately three times more likely to occur during pregnancy, primarily in the third trimester or immediately postpartum.
3. Steroids are probably effective if given within the first 5 to 7 days. Surgery is ineffective.

D. Other forms of cranial nerve palsy.
1. Cranial nerve IV: reported rarely to occur; mechanism similar to cranial nerve VII or VI palsy.
2. Cranial nerve VI: similar to above; usually resolve postpartum.

E. Meralgia paresthetica.
1. Causes numbness in the lateral aspect of the thigh.
2. Usually resolves within 3 months postpartum.

F. Sciatica and back pain. Lumbosacral disk surgery should be reserved only for progressive atrophy or bowel or bladder dysfunction.

G. Guillain–Barré's syndrome.
1. Causes are not generally affected by pregnancy.
2. Labor and delivery are otherwise normal.

IX. MYASTHENIA GRAVIS

A. Variable weakness and fatigability of skeletal muscles resulting from defective neuromuscular transmission (reduced acetylcholine receptors in the neuromuscular junction).

B. Does not affect labor progress, except for voluntary efforts in the second stage.

C. Certain drugs should be avoided, including the following:
1. Ester anesthetics: tetracaine (Pontocaine; Sanofi Winthrop, New York, NY, USA) and chloroprocaine (Nesacaine; AstraZeneca, Wilmington, DE, USA).
2. Curare (and other nondepolarizing muscle relaxants).
3. Halothane (Fluothane; Wyeth-Ayerst, Philadelphia, PA, USA).
4. Aminoglycoside antibiotics.
5. Quinine and quinidine.
6. Magnesium sulfate. The antidote with myasthenia is edrophonium (Tensilon; ICN, Costa Mesa, CA, USA), not calcium.

D. Treatment.
1. **Antepartum.**
   a. Pregnancy per se does not affect the severity of preexisting disease.
   b. Perinatal mortality is increased because of increased risk of premature delivery as well as neonatal myasthenia.
   c. Pharmacologic management of myasthenia gravis is not altered by pregnancy.
2. **Intrapartum.**
   a. Oral medications should be discontinued at the onset of labor and the intramuscular equivalents continued until oral medications can again be ingested. Equipotent dosages are as follows:
      (1) Neostigmine 0.5 mg intravenously.
      (2) Neostigmine 0.7 to 1.5 mg intramuscularly.
      (3) Neostigmine 15 mg by mouth.
      (4) Pyridostigmine 60 mg by mouth.
   b. Analgesia and anesthesia for labor require the utmost caution because of the risks of respiratory depression and aspiration.
   c. Myasthenia gravis does not affect the progress of labor and is not an indication for cesarean section.
3. **Postpartum.**
   a. Exacerbations are more likely to occur postpartum; tend to be sudden and severe in onset.
   b. Women with severe disease or whose babies have symptoms after nursing should not breast-feed.
   c. Most women return to preconceptional oral dosage with modest increases in dose to allow for the additional stresses of early parenthood.

E. Neonatal myasthenia.
1. Occurs in 10% to 15% of cases.
2. Results from transplacental transfer of maternal antibody against acetylcholine receptors.

X. MYOTONIC DYSTROPHY

A. Clinical characteristics.

1. Autosomal dominant; weakness and wasting in muscles of face, neck, and distal limbs; myotonia of hands and tongue.
2. Variable age at onset. The condition sometimes is diagnosed in mothers only after an affected child is born (these pregnancies are frequently complicated by polyhydramnios that results from poor fetal swallowing).
3. Predisposition to cardiac arrhythmia.
4. **Treatment.** There is none for the dystrophy. Severe myotonia: phenytoin (Dilantin; Pfizer, New York, NY, USA), quinine (FDA D), and procainamide (FDA D).

B. Effects on pregnancy.

1. Increased risk of spontaneous abortion.
2. Increased risk of premature labor and polyhydramnios, particularly with fetal involvement.
3. Normal first stage of labor.
4. Normal response to oxytocin.
5. Prolonged second stage of labor.

C. Labor management includes outlet forceps, regional anesthesia; avoid succinylcholine (can cause hyperthermia); nonpolarizing agents are generally safe.

XI. MOVEMENT DISORDERS

A. Restless legs the most common movement disorder in pregnancy. Treat with iron or folate.

B. Chorea Gravidarum—look for unmasking of another disorder (e.g., systemic lupus, Sydenham's chorea, etc.).

C. Parkinson's disease in pregnancy is rare because the age at which most patients have the disease is past childbearing years. However, pregnancy has been successfully accomplished in patients with Parkinson's disease.

1. Pregnancy may adversely affect Parkinson's in that there may be exacerbations soon after pregnancy.
2. Drugs used in Parkinson's disease:
   a. Levodopa (FDA C), MAO-B (selegiline, rasagiline—FDA C), dopamine agonists (pramipexole, ropinirole FDA C), and COMT inhibitor (entacapone FDA C).
   b. Amantadine (FDA C) can increase the risk of complications and malformations.

Recommended Readings

Adab N, Tudur SC, Vinten J, et al. Common antiepileptic drugs in pregnancy in women with epilepsy. *Cochrane Database Syst Rev*. 2004;(3):CD004848.

Argov Z, de Visser M. What we do not know about pregnancy in hereditary neuromuscular disorders. *Neuromuscul Disord*. 2009;19(10):675–679.

Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005.

Del Zotto E, Giossi A, Volonghi I, et al. Ischemic stroke during pregnancy and puerperium. *Stroke Res Treat*. 2011;2011:606780.

Dias MS, Sekhar LN. Intracranial hemorrhage from aneurysms and arteriovenous malformations during pregnancy and the puerperium. *Neurosurgery*. 1990;27:855–866.

Digre KB, Varner MW, Skalabrin E, et al. Diagnosis and treatment of cerebrovascular disorders in pregnancy. In: Adams HP, eds. *Handbook of Cerebrovascular Diseases*. New York, NY: Marcel-Dekker; 2005:805–850.

Goadsby PJ, Goldberg J, Silberstein SD. Migraine in pregnancy. *BMJ*. 2008;336:1502–1504.

Han IH. Pregnancy and spinal problems. *Curr Opin Obstet Gynecol*. 2010;22(6):477–481.

Harden CL, Hopp J, Ting TY, et al.; American Academy of Neurology; American Epilepsy Society. Management issues for women with epilepsy-focus on pregnancy (an evidence-based review): I. Obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50(5):1229–1236.

Harden CL, Meador KJ, Pennell PB, et al.; American Academy of Neurology; American Epilepsy Society. Management issues for women with epilepsy-focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2009;50(5):1237–1246.

Harden CL, Pennell PB, Koppel BS, et al.; American Academy of Neurology; American Epilepsy Society. Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009;73(2):142–149.

Kaplan PW. Neurologic aspects of eclampsia. *Neurol Clin*. 2004;22(4):841–861.

Lanska DJ, Kryscio RJ. Risk factors for peripartum and postpartum stroke and intracranial venous thrombosis. *Stroke*. 2000;31:1274–1282.

Lee AG, Pless M, Falardeau J, et al. The use of acetazolamide in idiopathic intracranial hypertension during pregnancy. *Am J Ophthalmol*. 2005;139(5):855–859.

Lee M, O'Brien P. Pregnancy and multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2008;79(12):1308–1311.

Loder E. Migraine in pregnancy. *Semin Neurol*. 2007;27(5):425–433.

Lynch JC, Gouvêa F, Emmerich JC, et al. Management strategy for brain tumour diagnosed during pregnancy. *Br J Neurosurg*. 2011;25(2):225–230.

Melhado EM, Maciel JA Jr, Guerreiro CA. Headache during gestation: evaluation of 1101 women. *Can J Neurol Sci*. 2007;34(2):187–192.

Menon R, Bushnell CD. Headache and pregnancy. *Neurologist*. 2008;14(2):108–119.

Micromedex. Version 2.0. Thompson Reuters. Nezvalová-Henriksen K, Spigset O, Nordeng H. Triptan exposure during pregnancy and the risk of major congenital malformations and adverse pregnancy outcomes: results from the Norwegian Mother and Child Cohort Study. *Headache*. 2010;50(4):563–575.

Oehm E, Hetzel A, Els T, et al. Cerebral hemodynamics and autoregulation in reversible posterior leukoencephalopathy syndrome caused by pre-/eclampsia. *Cerebrovasc Dis*. 2006;22(2–3):204–208.

Rudnik-Schoneborn S, Zerres K. Outcome in pregnancies complicated by myotonic dystrophy: a study of 31 patients and review of the literature. *Eur J Obstet Gynecol Reprod Biol*. 2004;114(1):44–53.

Sax TW, Rosenbaum RB. Neuromuscular disorders in pregnancy. *Muscle Nerve*. 2006;34(5):559–571.

Schlechte JA. Long-term management of prolactinomas. *J Clin Endocrinol Metab*. 2007;92(8):2861–2865.

Signore C, Spong CY, Krotoski D, et al. Pregnancy in women with physical disabilities. *Obstet Gynecol*. 2011;117:935–947.

Stafford IP, Dildy GA. Myasthenia gravis and pregnancy. *Clin Obstet Gynecol*. 2005;48(1):48–56.

Tang RA, Dorotheo EU, Schiffman JS, et al. Medical and surgical management of idiopathic intracranial hypertension in pregnancy. *Curr Neurol Neurosci Rep*. 2004;4(5):398–409.

Turan TN, Stern BJ. Stroke in pregnancy. *Neurol Clin*. 2004;22(4):821–840.

Wiese KM, Talkad A, Mathews M, et al. Intravenous recombinant tissue plasminogen activator in a pregnant woman with cardioembolic stroke. *Stroke*. 2006;37(8):2168–2169.

Winterbottom JB, Smyth RM, Jacoby A, et al. Preconception counselling for women with epilepsy to reduce adverse pregnancy outcome. *Cochrane Database Syst Rev*. 2008;(3):CD006645.

CHAPTER

58 The ABCs of Neurologic Emergencies

James D. Fleck and José Biller

This chapter is designed to be a very brief reference for common neurologic emergencies. In general, we presume an accurate diagnosis has been made and mainly concentrate on acute therapy. Although not comprehensive, this guide should allow you to care for a patient with the following problems for the first few hours.

I. ELEVATED INTRACRANIAL PRESSURE

A. Thirty degrees head-up neutral position.
B. Correction of factors exacerbating intracranial pressure (ICP).
1. Hypercarbia.
2. Hypoxia.
3. Hyperthermia.
4. Acidemia.
5. Hypotension.
6. Hypervolemia.
C. Avoid hypotonic solutions.
D. If ICP monitor has been placed, maintain cerebral perfusion pressure at 70 mm Hg.
E. Goal is euvolemia with elevation of osmolality.
F. Mannitol (20% solution) 1.0 g per kg intravenous (IV) as a bolus followed by 0.25 to 0.5 g per kg every 4 to 6 hours, depending on clinical status, serum osmolality (target 310 to 320 mOsm per kg), volume status, and ICP measurements.
G. Consider hypertonic saline 3% solution or 23.4% solution (0.5 to 2.0 cc per kg) through a central line in therapy-resistant elevation of ICP (target serum sodium of 145 to 155 mEq per L).
H. Dexamethasone (if vasogenic edema).
I. Hyperventilation to $PaCO_2$ of 30 to 35 mm Hg (temporizing measure).
1. Typically, it loses effectiveness in 24 to 48 hours.
2. Four percent change in cerebral blood flow for every 1 mm Hg change in $PaCO_2$.
J. Sedation and paralysis if necessary.
K. CSF drainage if necessary.
L. Barbiturates.
M. Hypothermia.
N. Surgical decompression (see Chapter 36).

II. COMA

A. Thorough general and neurologic examination.
B. ABCs: airway, breathing, and circulation.
C. IV fluids: normal saline.
D. Manage hypoglycemia with 50 ml of 50% glucose IV. Consider thiamine 100 mg IV before glucose.
E. Consider naloxone 0.4 to 2.0 mg IV for opioid overdose.
F. Consider flumazenil 0.2 mg IV for benzodiazepine overdose.
G. Arterial blood gases, glucose, electrolytes, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, liver enzymes, ammonia, CBC, urinalysis, blood and urine toxicology screens, and TSH.
H. If focal neurologic signs, or history of head trauma, consider therapy for elevated ICP with hyperventilation and osmotherapy.

I. Emergency brain imaging: typically unenhanced head CT.
J. Consider lumbar puncture (LP) if suspected CNS infection or suspected subarachnoid hemorrhage (SAH) with normal findings on head CT.
K. EEG.

III. STATUS EPILEPTICUS (GENERALIZED TONIC–CLONIC STATUS EPILEPTICUS)

A. ABCs: airway, breathing, and circulation.
B. IV line with normal saline.
C. Reduce temperatures >39°C with cooling blankets.
D. Consider 100 mg thiamine IV.
E. Consider 50 ml of 50% glucose IV.
F. Lorazepam 0.1 mg per kg IV at 2 mg per minute, maximum of 8 mg in adults *or* diazepam 0.2 mg per kg IV at 5 mg per minute up to a total dose of 20 mg.
G. Phenytoin 20 mg per kg IV (at <150 mg per minute in adults) or fosphenytoin 20 mg per kg IV (up to 150 mg phenytoin equivalent per minute).
H. If seizures continue, give additional bolus of phenytoin 10 mg per kg or fosphenytoin 10 mg per kg (to a maximum of 30 mg per kg).
I. Intubation, airway protection, and possibly ventilatory support.
J. If seizures persist, administer one of the following IV:
1. Midazolam (Load 0.2 mg per kg; repeat 0.2 to 0.4 mg per kg boluses every 5 minutes until seizure stops. Maximum loading dose 2 mg per kg.)
2. Propofol (Load 1 mg per kg; repeat 1 to 2 mg per kg boluses every 3 to 5 minute until seizures stop. Maximum loading dose 10 mg per kg.)
3. Valproate (Load 40 mg per kg over 10 minute. If seizures persist, 20 mg per kg over 5 minute.)
4. Phenobarbital (load 20 mg per kg, at 50 to 100 mg per minute).
K. If seizures still continue, use IV pentobarbital.
1. Loading with 5 to 10 mg per kg IV. Rate 50 mg per minute. Maintenance 1 to 3 mg/kg/hour.
2. Goal is burst-suppression pattern on EEG.
L. Management of intercurrent medical complications.

IV. BACTERIAL MENINGITIS

A. Treat within 30 minutes of arrival for medical care.
B. Manage elevated ICP.
C. Control seizures.
D. Manage complications (subdural empyema, brain abscess, ventriculitis, acute hydrocephalus, vasculitis, vascular spasm, venous thrombosis, and hyponatremia due to SIADH) (Fig. 58.1).
E. No universally accepted standard for duration of treatment.
F. Empiric antibiotic treatment of immunocompetent patients with community-acquired meningitis: ceftriaxone or cefotaxime *plus* vancomycin *plus* dexamethasone 0.15 mg per kg IV every 6 hours for 4 days (American Academy of Pediatrics recommendation for infants and children—first dose to be given before or within 4 hours of antibiotic). See Table 58.1 for antibiotic doses.
G. Consider ceftazidime if *Pseudomonas* infection is suspected.
H. Consider ampicillin if *Listeria* infection is suspected, as in an immunocompromised host.
I. Consider doxycycline if *Rickettsia*, *Anaplasma*, *Ehrlichia*, or *Coxiella burnetii* is suspected.
J. Chemoprophylaxis of meningococcal and *Haemophilus influenzae* infection with rifampin.

V. HERPES SIMPLEX ENCEPHALITIS

A. Fluid and ICP management.
B. Seizure control.

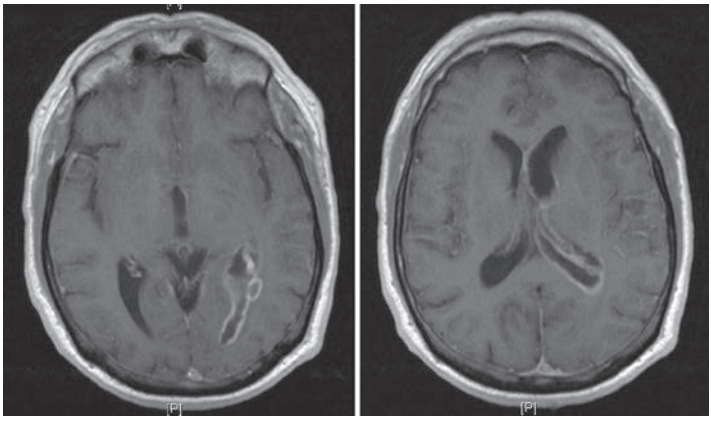


FIGURE 58.1 Axial T1-weighted MR images demonstrate diffuse abnormal enhancement extending along the ependymal surface of the left lateral ventricle and third ventricle consistent with ventriculitis/ependymitis in a 65-year-old man with Streptococcus constellatus meningitis.

TABLE 58.1 Antibiotic Therapy for Bacterial Meningitis

	Total Daily Dose (Dosing Interval)	
Antibiotics	**Adults**	**Children (Older than 2 Mo)**
Ceftriaxone	4 g (q12h)	100 mg/kg (q12h)
Cefotaxime	12 g (q4h)	300 mg/kg (q6h)
Vancomycin	2 g (q6h)	40–60 mg/kg (q6h)
Ceftazadime	6 g (q8h)	125–150 mg/kg (q8h)
Ampicillin	12 g (q4h)	200–300 mg/kg (q6h)

C. Acyclovir IV 10 mg per kg every 8 hours for 14 to 21 days; adjust dose to patient's renal function.
D. Untreated has a mortality rate of 70%.

VI. BRAIN ABSCESS

A. If there is no clear etiologic factor, administer ceftriaxone (Table 58.1) *plus* vancomycin (Table 58.1) *plus* metronidazole 500 mg every 6 hours in adults and 7.5 mg per kg every 8 hours in children.
B. Sulfa drugs for Nocardial infection.
C. Ceftazidime if Gram-negative aerobes are suspected.
D. Surgical treatment.

VII. CEREBRAL TOXOPLASMOSIS

A. Usually CD4 counts <200 cells per mm^3.
B. Pyrimethamine: loading dose of 100 to 200 mg then 75 to 100 mg per day *plus* folinic acid 10 to 15 mg per day *plus* sulfadiazine 6 to 8 mg per day.
C. If patient is allergic to sulfa drugs, substitute clindamycin 2,400 to 4,800 mg per day.

VIII. ISCHEMIC STROKE: WITHIN 3 HOURS OF ONSET

A. Unenhanced head CT does not show intracranial hemorrhage.
B. IV t-PA (Alteplase) 0.9 mg per kg, maximum dose of 90 mg. Ten percent of dose as initial bolus over 1 minute, and rest of dose infused over 60 minutes.

C. Exclusion criteria.
1. Minor or rapidly improving neurologic deficits (relative contraindication).
2. Seizure at the onset of symptoms (if residual impairments are postictal).
3. Symptoms suggestive of SAH.
4. Systolic blood pressure ≥185 mm Hg or diastolic blood pressure ≥110 mm Hg after two attempts to reduce blood pressure.
5. Stroke or serious head trauma in the previous 3 months.
6. Major surgery in the previous 14 days.
7. History of intracranial hemorrhage.
8. Gastrointestinal or genitourinary bleeding in the last 21 days.
9. Arterial puncture at a noncompressible site in the previous 7 days.
10. Received heparin therapy within the preceding 48 hours, and the aPTT is elevated.
11. INR >1.7 or prothrombin time (PT) >15 seconds.
12. Platelet count <100,000 per μl.
13. Glucose level <50 mg per dl (<2.7 mmol per L).
14. Myocardial infarction in the previous 3 months.

D. No antiplatelet agents or anticoagulants within first 24 hours of treatment.

E. Blood pressure must be maintained <180 per 105 mm Hg during and after treatment with tPA.

IX. ISCHEMIC STROKE 3 TO 4.5 HOURS FROM SYMPTOM ONSET

A. Exclusion criteria.
1. In addition to above (VIII C.) **exclusion criteria:**
   a. >80 years old.
   b. NIHSS >25.
   c. Combination of previous stroke and diabetes mellitus.
   d. On anticoagulant therapy regardless of INR.
   e. CT scan with low attenuation area of >one-third of the middle cerebral artery territory.

X. PERIOPERATIVE ACUTE ISCHEMIC STROKE WITHIN 14 DAYS OF SURGICAL PROCEDURE

A. IV thrombolysis contraindicated.

B. No CT exclusion.

C. Six hours in carotid artery territory.

D. Twelve hours or more in basilar artery occlusive disease.

E. Consider intra-arterial thrombolysis. IA tPA 1 to 5 mg bolus followed by 0.1 to 0.2 mg/kg/hour for 1 to 2 hours.

F. Consider mechanical clot disruption in high-risk surgery patients.

XI. MANAGEMENT OF INTRACRANIAL BLEEDING AFTER THROMBOLYTIC THERAPY

A. Stop infusion of thrombolytic.

B. Hematocrit, hemoglobin, PT/INR, aPTT, platelet count, fibrinogen, and type and cross match.

C. Emergency unenhanced head CT.

D. Ten units of cryoprecipitate containing factor VIII.

E. Six to eight units of platelets.

F. Hematology and neurosurgery consultations.

G. Surgery only after stabilization of intracranial bleeding.

XII. MANAGEMENT OF INTRACRANIAL BLEEDING ASSOCIATED WITH WARFARIN

A. Discontinue warfarin (Fig. 58.2).
B. Vitamin K_1 10 mg subcutaneously or 10 to 20 mg slow IV injection.
C. Fresh frozen plasma 10 to 15 ml per kg ***or*** prothrombin complex concentrate (15 to 50 units of factor IX per kg body weight) containing high concentrations of the vitamin K-dependent coagulation factors II, VII, IX, and X.
D. Neurosurgery consultation.
E. Recombinant FVIIa not routinely recommended.

XIII. MANAGEMENT OF INTRACRANIAL BLEEDING ASSOCIATED WITH HEPARIN

A. Discontinue heparin.
B. Protamine sulfate for every 1 mg/100/U of heparin administered in the preceding 4 hours.
C. Dose adjustment according to elapsed time from last heparin dose.
1. 20 to 60 minutes: 0.5 to 0.75 mg per 100 U of heparin.
2. 60 to 120 minutes: 0.375 to 0.5 mg per 100 U of heparin.
3. >120 minutes: 0.25 to 0.375 mg per 100 U of heparin.
D. Slow IV infusion; not to exceed 50 mg per 10 minute.

XIV. SUBARACHNOID HEMORRHAGE

A. Unenhanced head CT.
B. LP, if head CT is normal.
C. Four-vessel catheter cerebral angiography ***or*** CT angiography (less invasive alternative).
If renal insufficiency:
1. Normal saline 1 ml/kg/hour before and after angiography.
2. Acetylcisteine 600 mg orally twice daily for 2 days.
D. Blood pressure management (avoid nitroprusside/nitroglycerin; may use labetalol); maintain normotensive range.

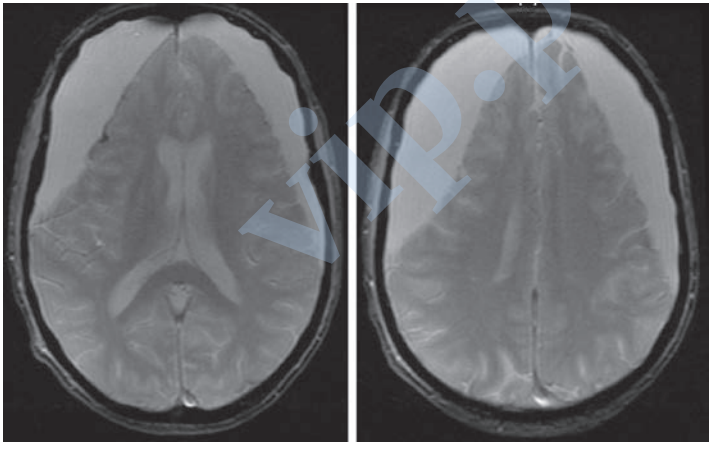


FIGURE 58.2 Axial gradient echo MRI shows large bilateral chronic subdural hematomas (SDH). The right-sided SDH is slightly larger than the left. There is approximately a 2 mm of right-to-left subfalcine shift. There is also evidence of previous hemorrhage along the lateral cortical surface of the right frontal lobe. The patient was an 83-year-old man with atrial fibrillation, on warfarin, who reported a subacute history of memory loss. INR on admission was 2.4.

E. Avoid hypotension and hypovolemia.
F. Nimodipine 60 mg every 4 hours by mouth or NG tube for 21 days.
G. Sedation, bedrest, analgesics, and stool softeners.
H. Prophylactic antiepileptic drugs (debatable).
I. Management of elevated ICP.
J. DVT prophylaxis.
1. Pneumatic compression boots.
2. May use subcutaneous UFH 5,000 units three times daily once aneurysm clipped.
K. Management of complications (rebleeding, hydrocephalus, vasospasm, and hyponatremia due to cerebral salt wasting or SIADH).
L. Antifibrinolytic therapy (epsilon aminocaproic acid or tranexamic acid) reduces risk of rebleeding but increases risk of cerebral ischemia.
M. Neurosurgery consultation (clipping versus coiling).

XV. CEREBELLAR HEMORRHAGE

A. ABCs: airway, breathing, and circulation.
B. Neurosurgery consultation (Fig. 58.3).
C. Ventriculostomy for acute hydrocephalus.
D. Consider craniotomy with removal of hemorrhage.

XVI. METASTATIC EPIDURAL SPINAL CORD COMPRESSION

A. Emergency MRI.
B. If MRI not available or contraindicated—CT myelography.
C. Dexamethasone: optimal dose uncertain (16 to 100 mg).
D. Radiation therapy (within 24 hours).

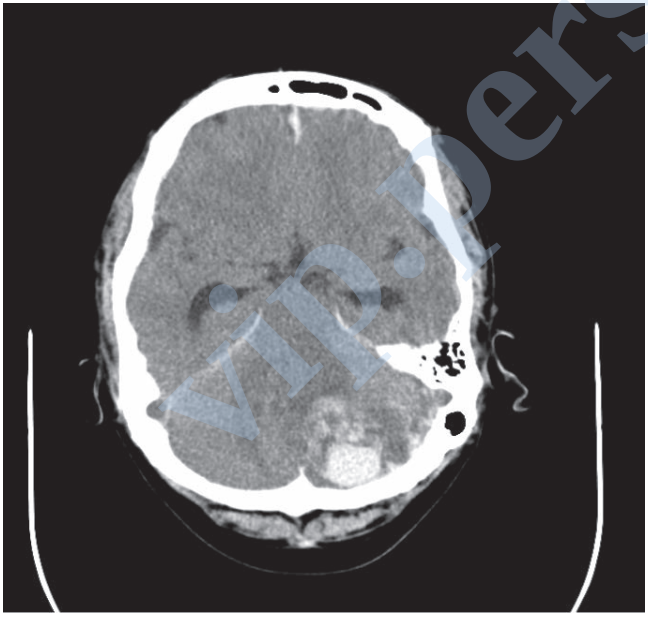


FIGURE 58.3 CT head without contrast demonstrates acute intraparenchymal hemorrhage of the left cerebellar hemisphere with effacement of the fourth ventricle and subsequent hydrocephalus of the third and lateral ventricles. The patient underwent placement of a right frontal external ventricular drain and a suboccipital craniotomy with bilateral decompression and removal of intracerebellar clot.

E. Consider surgical intervention:
1. If worsening deficits during or following radiotherapy.
2. If radioresistant tumor.
3. If spinal instability.
F. Pain control with opioids.
G. Venous thromboembolism prophylaxis for nonambulatory patients.
H. Bowel program.

XVII. CENTRAL CORD SYNDROME

A. Hyperextension traumatic injury in patients with longstanding cervical spondylosis.
B. **Other associations.**
1. Cervical spine fracture dislocations.
2. Congenital or acquired cervical canal stenosis.
3. Central spinal cord bleeding.
C. Disproportionate upper motor neuron pattern of weakness—upper limbs >> lower limbs.
D. Muscle stretch reflexes initially absent.
E. Bladder dysfunction.
F. Variable sensory loss below injury level.
G. IV methylprednisolone.
H. Surgery rarely indicated.
I. Favorable prognosis.

XVIII. GUILLAIN–BARRÉ SYNDROME

A. Nerve conduction studies including F waves.
B. CSF for albuminocytologic dissociation.
C. Endotracheal intubation if respiratory compromise: forced vital capacity (FVC) <15 ml per kg.
D. Monitoring for autonomic disturbances.
E. Plasma exchange: total 200 to 250 ml per kg over 1 to 2 weeks ***or*** immunoglobulin 0.4 g per kg IV per day for 5 days.

XIX. MYASTHENIC CRISIS

A. Careful monitoring of airway, swallowing, and respiration.
B. Intubation when FVC <15 ml per kg.
C. Optimize anticholinesterase dose.
1. If there is concern about anticholinesterase toxicity, stop anticholinesterase.
D. Manage concurrent infections.
E. Plasma exchange ***or*** immunoglobulin 0.4 g per kg IV a day for 5 days.

XX. ACUTE DYSTONIC REACTION

A. Stop causative agent.
B. Diphenhydramine 50 mg IV.
C. Benztropine 1 to 2 mg IV.
D. Typically follow with oral anticholinergic agent for 2 weeks, especially if long-acting dopamine receptor blocking agent was causative agent.

XXI. NEUROLEPTIC MALIGNANT SYNDROME

A. Immediate withdrawal of all neuroleptics or dopamine-depleting agents or reinstitution of previously withdrawn dopaminergic therapy.
B. Hydration and maintenance of adequate urine flow.

C. Alkalinization of urine if myoglobinuria.
D. Lowering of elevated body temperature.
E. Bromocriptine 2.5 to 5.0 mg four times a day, increase four times a day dose until response occurs (maximum 50 mg per day).
F. Dantrolene 1 to 10 mg per kg a day in divided doses.
G. Other possible agents for treatment include amantadine and carbamazepine.
H. For severe psychosis during treatment, consider electroconvulsive therapy.
I. Monitoring for complications.

XXII. ACUTE SEROTONIN SYNDROME

A. Discontinue all serotonergic drugs.
B. Benzodiazepines—especially for agitation.
C. Cyproheptadine 12 to 32 mg per day. Consider initial dose in adults of 12 mg and maintenance dose of 8 mg every 6 hours.
D. Other possible treatments include propranolol, chlorpromazine, and methysergide (not available in the United States).
E. Monitoring for complications.

XXIII. GIANT CELL ARTERITIS, TEMPORAL ARTERITIS

A. STAT erythrocyte sedimentation rate.
B. Oral prednisone 1 to 2 mg per kg every day ***or*** 1 g per day methylprednisolone IV for 3 days followed by oral prednisone 1 mg per kg a day, especially if there are visual symptoms or visual loss.
C. Long segment superficial temporal artery biopsy.

XXIV. CENTRAL RETINAL ARTERY OCCLUSION

A. Ocular massage.
B. Breathing 95% oxygen and 5% carbon dioxide.
C. Lowering of intraocular pressure with acetazolamide intravenously or orally.
D. Anterior chamber paracentesis.
E. Aspirin.
F. Consider intraarterial thrombolysis (<12 hours).

XXV. WERNICKE'S ENCEPHALOPATHY

A. Thiamine deficiency state—chronic alcoholism, hyperemesis gravidarum, starvation, gastrointestinal malignancies, pyloric stenosis, anorexia nervosa, inappropriate parenteral nutrition, digitalis intoxication, chronic hemodialysis, drug therapy for obesity, and thyrotoxicosis.
B. Global confusional state.
C. Ataxic gait.
D. Ocular abnormalities.
1. Nystagmus.
2. CN VI palsy.
3. Gaze palsy.
4. Vestibular paresis.
E. 100 mg thiamine IV.
F. Bed rest.
G. Nutritional supplements.
H. Avoid glucose without thiamine.

Recommended Readings

Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. American Heart Association/American Stroke Association Stroke Council; American Heart Association/American Stroke Association Clinical Cardiology Council; American Heart Association/American Stroke Association Cardiovascular Radiology, and Intervention Council; Atherosclerotic Peripheral Vascular Disease Working Group; Quality of Care Outcomes in Research Interdisciplinary Working Group. *Stroke.* 2007;38(5):1655–1711.

Benderson JB,Connolly ES Jr, Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke*. 2009;40(3):994–1025.

Biller J, Chair. Asconapé J, Kase CS, et al. Iatrogenic neurology. *Continuum.* 2001;7:1–224.

Caroff SN, Campbell EC, Sullivan KA. Neuroleptic malignant syndrome in elderly patients. *Expert Rev Neurotherapeutics.* 2007;7(4):423–431.

Chamberlain MC, Kornanik PA. Epidural spinal cord compression: a single institution's retrospective experience. *Neuro-oncology.* 2000;192:120–123.

Diringer MN, Zazulia AR. Osmotic therapy: fact and fiction. *Neurocrit Care*. 2004;1:219–233.

Johnson RT, Griffin JW, eds. *Current Therapy in Neurologic Disease.* 5th ed. St Louis, MO: Mosby; 1997.

Morgenstern LB, Hemphill JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for health professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41:2108–2129.

Qureshi Al, Thurim S, Broderick JP, et al. Spontaneous intracerebral hemorrhage. *N Engl J Med*. 2001;344:1450–1460.

Rabinstein AA, Wijdicks E. *Tough Calls in Acute Neurology*. Boston, MA: Butterworth-Heinemann; 2004.

Roos K, ed. *Central Nervous System Infectious Diseases and Therapy*. New York, NY: Marcel Dekker; 1997.

Ropper AH, ed. *Neurological and Neurosurgical Intensive Care*. 3rd ed. New York, NY: Raven Press; 1993.

Rosovsky RP, Crowther MA. What is the evidence for the off-label use of recombinant Factor VIIIa (rFVIIa) in the acute reversal of warfarin? ASH evidence-based review 2008. *Hematology Am Soc Hematol Educ Program*. 2008:36–38.

Stochetti N, Maas AL, Chieregato A, van der Plas AA. Hyperventilation in head injury: a review. *Chest*. 2005;127:1812–1827.

Wasterlain CG, Treiman DM, eds. *Status Epileptic Mechanisms and Management*. Cambridge, MA: MIT Press;2006.

Wijdicks E. *Neurologic Catastrophes in the Emergency Department.* Boston, MA: Butterworth-Heineman; 2000.

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