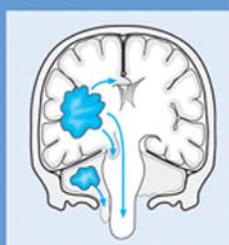
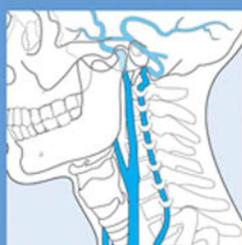
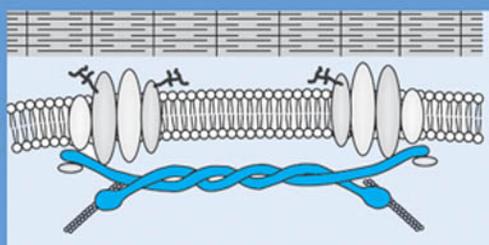
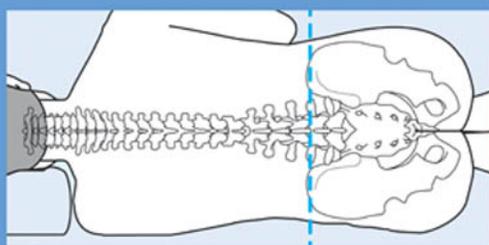
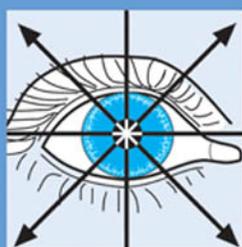
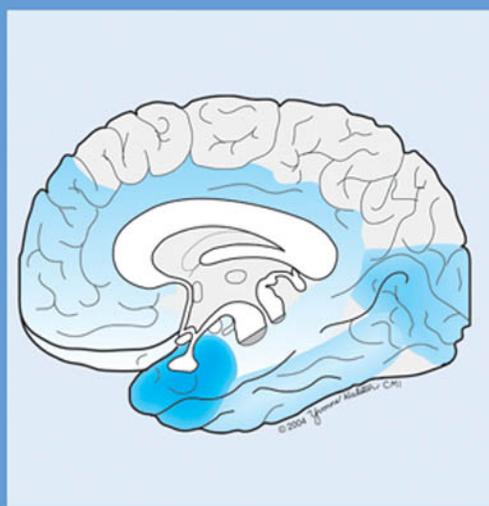
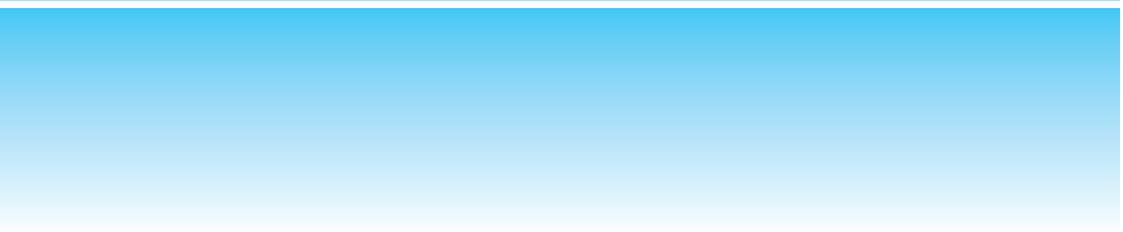


# Fundamentals *of* Neurologic Disease



Larry E. Davis, Molly K. King  
Jessica L. Schultz

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# Fundamentals of Neurologic Disease

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# Preface

This textbook is intended for students who wish to learn the basic principles of neurology and to understand common neurologic diseases. We selected 58 neurologic diseases based on their frequency, ability to represent that category of neurologic disease, value in teaching neuroscience concepts, and diagnostic importance.

We recognized that most introductory courses on neurologic diseases are short and lack sufficient time for a student to extensively read a comprehensive neurology textbook. In addition, while abbreviated versions of neurology textbooks cover a myriad of neurologic diseases in telegraphic style, they are difficult to comprehend unless one already knows about the disease. Thus, many students finish the course with a spotty understanding of neurology. We designed our book to be read from cover to cover, giving the reader a more thorough understanding of the fundamentals of neurology.

The first chapters cover the basic approach a neurologist takes when encountering a patient with a neurologic problem, the key elements of the neurologic exam, and an overview of common neurologic tests. We discuss how to use the history and neurologic exam to localize the patient's problem to specific neuroanatomic site(s) and to use the neuroanatomic information along with results of appropriate laboratory tests to establish a diagnosis.

The later chapters are divided into chapters that review common diseases present at different neuroanatomic sites along the neuroaxis from muscle to the cerebral cortex and chapters on diseases that have a similar pathophysiology. Each chapter begins with an overview to understand the common features of this group of diseases. Selected diseases are then discussed with an emphasis on the pathophysiology, major clinical features, major laboratory findings, and the principles of disease management. Our book covers both adult and pediatric neurologic diseases.

This book does not cover detailed aspects of disease variants, all possible laboratory tests, drug dosages, or many related neurologic diseases as it is not designed for the specific treatment of neurologic patients. Our goal is to provide broad and integrated coverage of the fundamentals of common neurologic diseases in the context of a competent examination strategy, the disease pathophysiology, and the principles of disease management. We hope that students will find the book structure and context useful in their studies and that it will contribute to the instructors' efforts to support students in their learning.

*Larry E. Davis, M.D.*  
*Molly K. King, M.D.*  
*Jessica L. Schultz, M.D.*

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# Foreword

A detailed patient history and physical examination remain the underpinnings of neurologic diagnosis. Imaging and laboratory testing are important, but the ability to piece together clues in the patient's story and to localize lesions by the findings on the neurologic examination still separate the good neurologist from the main body of physicians. Medical students who choose neurology for a career often cite two factors that have influenced them—first, the spectacular basic and clinical advances in the understanding and treatment of neurologic illnesses and, second, the continued reliance on clinical skills and the formulation of diagnoses at the bedside or in the clinic.

This condensed volume introduces the reader to neurologic diseases; it emphasizes the clinical

anatomical and pathological correlation and provides many tables and line drawings that help in understanding the anatomy and physiological basis of disease and the differential diagnosis of neurologic illnesses. Too often introductory volumes on neurology are overwhelming in bulk and complexity. The authors of this volume have succeeded in presenting a gentler and concise introduction to this fascinating subject.

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## Steps in Diagnosing Neurologic Conditions

1. Determine whether the condition involves the nervous system
2. Determine an anatomic localization
3. Establish the time course of symptoms
4. Determine the most likely disease category(s)
5. Make a clinical diagnosis or differential diagnoses
6. Order appropriate laboratory or neuroimaging tests
7. Establish definite diagnosis
8. Begin appropriate etiologic and symptomatic treatment

### 1. Determine Whether the Condition Involves the Nervous System

The first step is to determine whether the patient's signs and symptoms are due to an illness involving the nervous system. This decision is based on the history and physical exam coupled with knowledge of general medical diseases. For example, syncope causes loss of consciousness, but the etiology can be from cardiovascular disease.

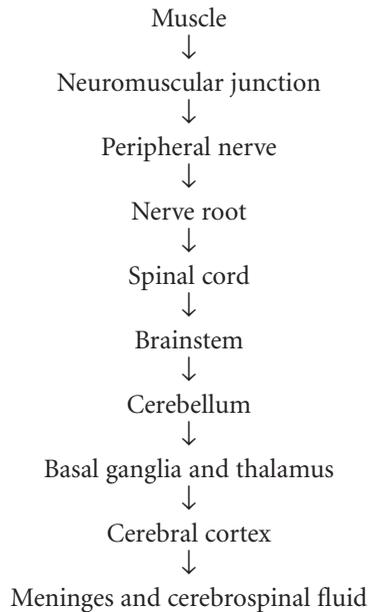
### 2. Determine an Anatomic Localization

Another important step based on the history and physical examination is to establish the most likely neuroanatomic site that could cause the patient's problem. While experts may bypass this step, it is helpful to the beginning clinician. Knowledge of the site enables the clinician to narrow the list of differential diagnoses and to determine which laboratory and neuroimaging tests will yield the most useful information.

Neurologic localization is possible because the nervous system is organized such that each major neuroanatomic location gives rise to specific signs and symptoms. As such, the nervous system differs from many other organs such as the liver,

in which damage to any lobe produces similar symptoms.

The nervous system can be divided into discrete anatomic compartments that give rise to a specific constellation of signs and symptoms. This book follows the neuroanatomic outline below:



In defining the neuroanatomic site, the clinician should establish the highest and lowest points of the nervous system that can give rise to the patient's signs and symptoms. Helpful keys in determining the most likely neuroanatomic localized site include:

1. Finding the earliest signs and symptoms of the illness, which usually denote anatomically where the disease began.
2. Determining the anatomic site where weakness and/or sensory changes likely are produced. Motor and sensory systems are multisynaptic long-tract systems commonly involved in many diseases. Weakness produced by dysfunction of the motor system at the motor cortex, brainstem, spinal cord, peripheral nerves, neuromuscular junctions, and muscle has unique characteristics that help localize the site of the problem.
3. Identifying accompanying nonneurologic signs and symptoms that may help localize the site.

Although there are many neurologic signs and symptoms that point to a given neuroanatomic site, some of the more common clinical features are provided in Table 1-1. However, not all the signs and symptoms are present in a given patient, and certain diseases do not follow those specified in this table.

### 3. Establish the Time Course of Symptoms

The time course of the patient's symptoms is an important part of the history and can be difficult to obtain. The patient often may not have recognized early symptoms or attributed them to other causes. Patients also rarely describe their symptoms in a clear time line. Determination of the time course helps with urgency of the work-up, disease category classification, and prognosis. In children it is often difficult to determine whether the disease is progressive or static. Static lesions may be misinterpreted as progressive when children fail to reach their expected age-related milestones.

### 4. Determine the Most Likely Disease Etiology(s)

Most neurologic diseases fall into one disease category, and each category has common clinical features that allow selection of the category. Below are useful questions to establish the most likely disease category:

- Is the problem new or has it occurred in the past?
- Was there a trigger for the onset or episode?
- What aggravates and alleviates the symptoms?
- Was onset acute, subacute, or gradual?
- Are signs rapidly progressive over hours to 2 days, subacutely progressive over days to a few weeks, slowly progressive over months to years, or static and not progressive?
- Are signs unilateral or bilateral?
- Is pain a feature, what are its characteristics, and where is it located?
- Is there a family history of similar problems?
- Is lesion likely a mass or nonmass?
- Is the location focal, multifocal, or diffuse?

Applying the acronym VINDICATES is one way to classify etiologic groups. Table 1-2 lists common clinical features seen in each category. Again, diseases in each category may not express all the features.

### 5. Make a Clinical Diagnosis or Differential Diagnoses

At this point the clinician uses the information gained from the history and neurologic examination, most likely disease category, and knowledge of neuroanatomy and neurophysiology to establish a clinical diagnosis or list of relevant differential diagnoses. In essence, the clinical diagnosis is a working diagnosis that allows the clinician to determine which laboratory or neuroimaging tests, if any, are necessary for establishing a definite diagnosis. While this book gives the reader considerable basic information about common neurologic diseases, the reader should refer to journal articles and comprehensive neurology textbooks for complete information on specific diseases and details about treatment.

The differential diagnosis should focus on diagnoses considered most likely. The adage, "Think of horses, not zebras, when you hear hoof beats, unless you are in Africa" is true in neurology. Common diagnoses are common but may present with atypical features. The differential diagnosis list should contain diseases that you intend to rule in or out by appropriate laboratory tests. One can always add more diseases to the differential diagnosis list as the work-up proceeds.

### 6. Order Appropriate Laboratory and/or Neuroimaging Tests

Neurologic tests should serve to: (1) establish the etiologic diagnosis when several likely diagnoses exist; (2) help make therapeutic decisions; and (3) aid in following the results of treatment. Knowledge of the approximate neuroanatomic location and the most likely category of disease process enables the clinician to order appropriate tests. As neurologic tests are expensive, time-consuming and occasionally dangerous or uncomfortable to the patient, thought must be given before ordering.

**Table 1-1 Common Clinical Features of Neurologic Illness by Neuroanatomic Site**

<p><b>Muscle</b></p> <ul style="list-style-type: none"> <li>Weakness without sensory loss</li> <li>Proximal muscles weaker than distal muscles</li> <li>Weakness that is often slowly progressive</li> <li>Muscle atrophy</li> </ul>
<p><b>Neuromuscular Junction</b></p> <ul style="list-style-type: none"> <li>Fatigue (especially to chewing and in proximal limb muscles)</li> <li>Weakness without sensory loss</li> <li>Ptosis with changing diplopia</li> <li>No muscle atrophy</li> </ul>
<p><b>Peripheral Nerve</b></p> <ul style="list-style-type: none"> <li>Mixture of motor and sensory findings</li> <li>Distribution of signs either in a single nerve or in many nerves</li> <li>Distal limb signs more pronounced than proximal signs</li> <li>Trunk uncommonly involved</li> <li>Pain in feet or along a single nerve distribution</li> <li>Sensory loss due to pain and temperature, or vibration and position sense, or to all modalities</li> <li>Muscle atrophy and occasionally fasciculations corresponding to involved nerve</li> </ul>
<p><b>Nerve Root</b></p> <ul style="list-style-type: none"> <li>Dermatomal distribution of sensory loss</li> <li>Neck or back pain that may extend into limb</li> <li>Loss of deep tendon reflex associated with that root</li> <li>Weakness only in muscles supplied by that root</li> </ul>
<p><b>Spinal Cord</b></p> <ul style="list-style-type: none"> <li>Sensory level is present</li> <li>Weakness that may involve both legs or all limbs</li> <li>Bowel and bladder signs</li> <li>Autonomic nervous system dysfunction</li> <li>Loss of reflexes at the level of cord involvement with hyperactivity below that level</li> <li>Babinski signs</li> <li>Leg spasticity</li> </ul>
<p><b>Brainstem</b></p> <ul style="list-style-type: none"> <li>Cranial nerve involvement (especially facial weakness, facial sensory loss, dysphagia, dysarthria, hoarseness, and diplopia)</li> <li>Vertigo</li> <li>Tetraparesis with four limb weakness and spasticity</li> <li>Coma or semicoma</li> <li>Changes in blood pressure, heart rate, and respiratory rate</li> </ul>
<p><b>Cerebellum</b></p> <ul style="list-style-type: none"> <li>Ataxia of limbs and gait</li> <li>Vertigo</li> <li>Nystagmus</li> </ul>
<p><b>Basal Ganglia and Thalamus</b></p> <ul style="list-style-type: none"> <li>Extrapyramidal signs (bradykinesia, shuffling gait, masked facies, etc.)</li> <li>Movement disorder (chorea, athetosis, or tremor, which may be unilateral or bilateral)</li> </ul>
<p><b>Cerebral Cortex</b></p> <ul style="list-style-type: none"> <li>Unilateral focal neurologic signs such as hemiparesis, hemihypesthesia, homonymous hemianopia</li> <li>Aphasia</li> <li>Memory loss</li> <li>Apraxia</li> <li>Dementia</li> <li>Seizures</li> </ul>
<p><b>Meninges and Cerebrospinal Fluid</b></p> <ul style="list-style-type: none"> <li>Headache—usually diffuse</li> <li>Meningismus</li> <li>Cranial nerve signs—often with multiple nerves involved</li> </ul>

**Table 1-2 Common Clinical Features of Neurologic Illness by Etiologic Group**

<p><b>Vascular</b></p> <ul style="list-style-type: none"> <li>Sudden onset</li> <li>Asymmetrical signs</li> <li>Symptoms worse at beginning and then improve</li> <li>Hemiparesis and hemihypesthesia (but not anesthesia) common</li> </ul>
<p><b>Inflammatory/Infectious</b></p> <ul style="list-style-type: none"> <li>Fairly rapid onset and progression</li> <li>Fever common</li> <li>Signs usually involving meninges or cerebral cortex</li> <li>White blood cell count and erythrocyte sedimentation rate elevated</li> </ul>
<p><b>Neoplastic</b></p> <ul style="list-style-type: none"> <li>Slowly progressive</li> <li>In adults, mainly involving cerebral cortex, while in children, mainly involving cerebellum and brainstem</li> <li>Unilateral focal signs common early in disease</li> </ul>
<p><b>Degenerative/Hereditary</b></p> <ul style="list-style-type: none"> <li>Slowly progressive</li> <li>Symmetrical signs</li> <li>Diffuse signs</li> <li>Pain seldom prominent</li> <li>Family history of similar illness may be present</li> <li>Clinical features varying, but often including dementia, parkinsonism, and weakness</li> </ul>
<p><b>Intoxication or Withdrawal</b></p> <ul style="list-style-type: none"> <li>Gradual onset of symptoms over hours to weeks</li> <li>History of unusual drug or substance usage</li> <li>Altered mental activity (confusion, delirium, stupor, or coma)</li> <li>Distal symmetrical polyneuropathy common</li> <li>Focal neurologic signs less common</li> </ul>
<p><b>Congenital/Developmental</b></p> <ul style="list-style-type: none"> <li>Present at birth or early childhood</li> <li>Family history of similar disease common</li> <li>Mainly static but can appear progressive in childhood as child fails to gain developmental milestones</li> <li>Mental retardation, seizures, and spasticity common</li> </ul>
<p><b>Autoimmune/Demyelinating</b></p> <ul style="list-style-type: none"> <li>Onset over days</li> <li>Prominent motor, sensory, visual, and/or cerebellar signs common</li> <li>Symmetrical or diffuse clinical features</li> </ul>
<p><b>Trauma</b></p> <ul style="list-style-type: none"> <li>Abrupt onset</li> <li>History of trauma present</li> <li>Coma or loss of consciousness common</li> <li>May cause motor and sensory dysfunction of one peripheral nerve</li> <li>Clinical improvement eventually occurs</li> </ul>
<p><b>Endocrine/Metabolic</b></p> <ul style="list-style-type: none"> <li>Gradual onset</li> <li>Slowly progressive</li> <li>Systemic disease common, especially in liver, lung, or kidney</li> <li>Symmetrical signs</li> <li>Abnormal lactation common</li> </ul>
<p><b>Social/Psychologic</b></p> <ul style="list-style-type: none"> <li>Past or present history of psychiatric illness, especially depression</li> <li>History of abuse</li> <li>Waxing and waning of symptoms</li> <li>Nonphysiologic exam</li> <li>Secondary gain</li> <li>Positive review of systems with multiple somatic complaints</li> </ul>

The overall goal should be to establish the diagnosis efficiently in both time and money. The shotgun approach (where many tests are ordered in hopes of finding the diagnosis) is both expensive and often unhelpful.

## 7. Establish Definite Diagnosis

The definite or etiologic diagnosis implies that the diagnosis is firm and no further diagnostic tests are indicated. Combining information gained from the history and physical exam, the results of appropriate laboratory and neuroimaging tests, and knowledge of the anatomy and pathophysiology of the disease in question helps the clinician arrive at the definite diagnosis. For some diseases, there may be a single diagnostic test that establishes the etiology. For example, growth of *Streptococcus pneumoniae* from the cerebrospinal fluid of a patient with meningial symptoms establishes the definite diagnosis of pneumococcal bacterial meningitis. For other diseases, for example, classic migraine headache, there may be no diagnostic test that establishes the etiology and definite diagnosis must rest on the history, physical exam, and knowledge of the disease in question.

## 8. Begin Appropriate Etiologic and Symptomatic Treatment

Treatment of neurologic disease differs from treatment of diseases of other organs in several aspects. First, neurons do not divide after birth. Thus the brain cannot replace lost neurons. Second, damaged central nervous system (CNS) myelin or oligodendrocytes have limited ability to remyelinate naked axon segments. Third, surgical removal of a brain lesion may not be possible because the lesion is in part of the brain that is inaccessible due to its deep anatomic location or because the lesion is surrounded by critical brain areas (eloquent brain). Fourth, any drugs given systemically to the patient must be capable of crossing the blood–brain barrier. This barrier severely limits many otherwise effective medications that could be given to the patient. Even if the drugs were given intrathecally into the cerebrospinal fluid (CSF) space to bypass the

blood–brain barrier, they would have difficulty diffusing any distance into the cerebral cortex.

Management of the patient with a neurologic disease can be divided into four categories: prevention, etiologic treatment, symptomatic treatment, and rehabilitation. The key to success is management of the patient's complaints and not just the laboratory tests.

### Prevention

“An ounce of prevention is worth a pound of cure” is particularly pertinent in neurologic disease. A major effort in neurology focuses on early disease detection and prompt treatment to minimize later complications. For example, the treatment of hypertension markedly reduces the incidence of subsequent strokes. Treatment of the patient with a transient ischemic attack with aspirin reduces future strokes in many patients by 13–20%. Immunization of children with poliovirus vaccine prevents subsequent paralytic poliomyelitis.

### Etiologic Treatment

Treatment of the etiology should be the goal in the care of every patient. Often it is possible to reverse or halt the underlying disease process. This may cure the patient, such as by removal of a meningioma. Once the etiology is established, current treatment options are easily found in standard medical or neurologic textbooks or recent review articles in journals. Unfortunately, for many neurologic diseases the etiologies are unknown, and hence treatment options are poor.

### Symptomatic Treatment

Treatment should be aimed not only at the etiology but also at relieving the patient's signs and symptoms, as they are what brought the patient to the doctor. Symptomatic treatment often brings considerable improvement in the quality of the patient's life. For example, administration of L-dopa greatly improves the disturbing features of Parkinson's disease. However, symptomatic treatment is not etiologic treatment. While L-Dopa improves the symptoms of Parkinson's disease, it does not halt disease progression. Similarly, narcotics relieve the pain of a brain tumor but do not

cure the tumor. When treating the patient, it is important to observe for side effects.

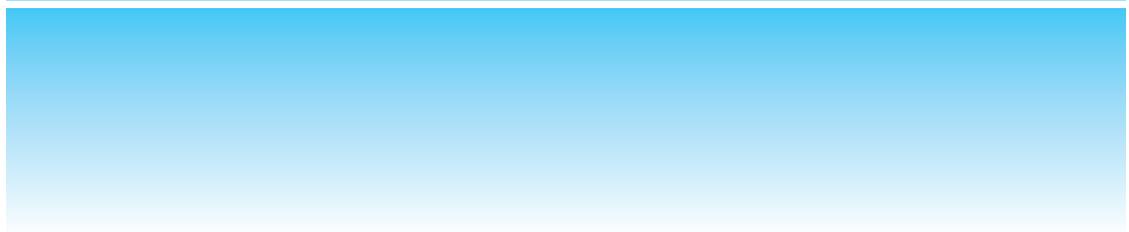
Symptomatic treatment should also address the psychologic aspects of the illness. Fear or worry about the disease frequently causes anxiety or depression that may incapacitate the patient. Even if the disease cannot be cured and is fatal, the patient should know that the physician cares and will do everything possible to minimize symptoms.

### **Neurorehabilitation**

Neurorehabilitation should not be overlooked as an important therapeutic tool in the care of the neurologic patient. We are becoming increasingly

aware that the brain has considerable capacity for recovery from damage. There are many factors involved in recovery. An important one is neuroplasticity. The term neuroplasticity means that other neuronal populations take over the function of the damaged part of the brain. At present we have little understanding of how the brain can alter synaptic pathways to accomplish this. In general, children have a greater capacity than adults for neuroplasticity. Increasing evidence suggests that it can be enhanced through active stimulation, motivation, and rehabilitation of the patient. In addition, rehabilitation can help the patient learn new methods to compensate.

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## 2 NEUROLOGIC EXAMINATION

### Overview

The physical examination begins the instant you meet the neurologic patient. Much information is gleaned from observing the patient during the interview and noting the patient's speech pattern, mentation (mental activity), behavior, and presence of abnormal motor movements. The neurologic exam is divided into specific components that are usually written separately in the chart. Below are the neurologic tests commonly done. For each area there are many additional tests that can be done (see comprehensive neurology textbooks for details).

### Mental Status Examination

The depth to which the mental status exam is pursued depends on the presenting problem and your observations while taking the history. Components of the mental status exam include: alertness, attention, cooperation, memory, cognition, mood and affect, and speech and language.

*Alertness, attention, and cooperation* are evaluated during the history. If the patient fails to demonstrate the ability to attend, stay awake, or

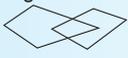
cooperate, the remainder of the mental status exam should be interpreted cautiously. For example, problems with memory may be due to the fact that the patient never paid attention to the information presented.

*Memory* problems are suggested by a vague imprecise history, inability to recall current events, or not remembering the events of the day. One can ask the patient to repeat three objects (like apple, table, and penny) immediately and then after 5 minutes. Normal subjects usually can repeat at least two of the objects at 5 minutes, especially with prompting.

*Cognition* should be evaluated relative to the patient's education and socioeconomic background. In general terms, it is an estimate of the patient's general mental capability that includes reasoning, planning, solving problems, thinking abstractly, comprehending complex ideas, learning quickly, and learning from experience. If a deficit is detected, critical questions include whether it is of recent onset, or progressive, or static.

One useful screening test of mental status is called the Folstein Mini Mental Status Examination (Table 2-1). This test is not sensitive for mild cognitive impairment, as scores as low as 22/30 may be normal depending on education and socioeconomic background.

Table 2-1 *Folstein Mini Mental Status Examination*

Task	Instructions	Scoring
Date Orientation	“Tell me the date?” Ask for omitted items.	One point each for year, season, date, day of week, and month 5
Place Orientation	“Where are you?” Ask for omitted items.	One point each for state, county, town, building, and floor or room 5
Register three Objects	Name three objects slowly and clearly. Ask the patient to repeat them.	One point for each item correctly repeated 3
Serial Sevens	Ask the patient to count backward from 100 by 7. Stop after five answers. (Or ask them to spell “world” backwards.)	One point for each correct answer (or letter) 5
Recall three Objects	Ask the patient to recall the objects mentioned above.	One point for each item correctly remembered 3
Naming	Point to your watch and ask the patient “What is this?” Repeat with a pencil.	One point for each correct answer 2
Repeating a Phrase	Ask the patient to say “No ifs, ands, or buts.”	One point if successful on first try 1
Verbal Commands	Give the patient a plain piece of paper and say, “Take this paper in your right hand, fold it in half, and put it on the floor.”	One point for each correct action 3
Written Commands	Show the patient a piece of paper with “CLOSE YOUR EYES” printed on it.	One point if the patient’s eyes close 1
Writing	Ask the patient to write a sentence.	One point if sentence has a subject, a verb, and makes sense 1
Drawing	Ask the patient to copy a pair of intersecting pentagons onto a piece of paper. 	One point if the figure has ten corners and two intersecting lines 1
<b>Scoring</b>	A score of 24 or above is considered normal.	<b>30</b>

Adapted from Folstein et al. Mini Mental State. *J Psych Res* 1975;12:196–198.

Important *moods* and *affects* to note are depression and inappropriate jocular behavior. Symptoms of depression often include somatic complaints. Inappropriate affect may suggest frontal lobe dysfunction.

*Speech* and *language* abnormalities are divided into dysarthria and dysphasia. Dysarthria results from poor articulation—like talking with rocks in your mouth. The sentence makes sense but the sound is garbled. Abnormalities of the mouth (poor dentition) or of cranial nerves (CNs) IX, X, and XII are common causes. Dysarthria does not affect the ability to write or read. Dysphasia implies dysfunction in understanding or forming sentences. In expressive aphasia, the patient often speaks short, truncated sentences without adjectives

or adverbs and has garbled speech. Receptive aphasia usually produces normal-sounding speech but the content does not make sense relative to the question. In both aphasias, there is difficulty in repeating phrases such as “No ifs, ands, or buts.” Aphasia affects ability to write and read. Language abnormalities and apraxias are covered in Chapter 11, “Disorders of Higher Cortical Function.”

## Cranial Nerve Examination

### CN I

*Olfactory nerves* are seldom routinely tested unless a patient has a complaint of poor taste or smell, or

a history suggesting problems with frontal lobes or facial bones. First, ensure there are no obstructions in the nasal passages by inspection with an otoscope. Smell cannot be tested in each side since both sides of the nose communicate. Ask the patient to close his or her eyes and identify whether he or she can smell an odor and then identify the odor's name. Common substances such as coffee grounds, unlit cigarettes, and perfumed soap are convenient to use in testing. Alcohol and ammonia should not be used, as these odors stimulate CN V and give a false-positive test.

## CN II

*Optic nerve* function is usually divided into visual acuity, visual fields, and fundoscopic exam. To test the patient's visual acuity in each eye while wearing their glasses, one can use a Snellen eye chart or a near-vision card. The ability to read standard newsprint suggests 20/40 or better acuity. If the patient's glasses are not available, a pinhole card (paper with pin pushed through the center) can improve vision. If visual acuity is 20/50 or better, the problem is usually ocular and not neurologic.

Visual fields are evaluated by confrontation testing each eye separately. Having the patient stand about 4 feet away with one eye closed and looking at your nose, ask him or her to count the number of fingers (one, two, or five) presented in the four visual quadrants. Confrontational testing detects a homonymous hemianopia or quadranopia but not constriction of visual fields from glaucoma.

On fundoscopic examination, carefully observe the retinal vessels for hemorrhages and exudates and

then follow them into the optic disc itself. Color and size of the disc and the presence of papilledema are particularly important. Papilledema is suggested by swollen optic disc heads with the margins appearing blurred or raised, with reasonable vision in that eye.

Pupil size and the light reflex involve CN II and autonomic eye nerves. Observe the pupils in dim light with illumination from below. The pupils should be round and be within 1 mm of each other in size and constrict equally when the patient attempts to look at his or her nose (accommodate). Anisocoria or unequal pupil sizes signifies dysfunction of either the sympathetic nerve (small pupil or miosis) or parasympathetic nerve (large pupil or mydriasis). In the light reflex, one tests a direct light reflex (the pupil constricts when a light is shined into it) and then a consensual reflex (the opposite pupil constricts when a light is shined into the other eye). Both pupils should constrict briskly and equally to light. Shining the light into one eye and failing to see both pupils constrict implies ipsilateral retina or CN II dysfunction; failure of the ipsilateral iris to constrict implies dysfunction of the ipsilateral sympathetic nerve; and failure of the contralateral pupil to constrict suggests dysfunction of the contralateral sympathetic nerve.

## CNs III, IV, and VI

*Oculomotor, trochlear, and abducens nerves* innervate the extraocular eye muscles. They are evaluated by observing eye movement when the patient is asked to follow your finger in all nine directions of gaze (Figure 2-1). Observe whether the eye

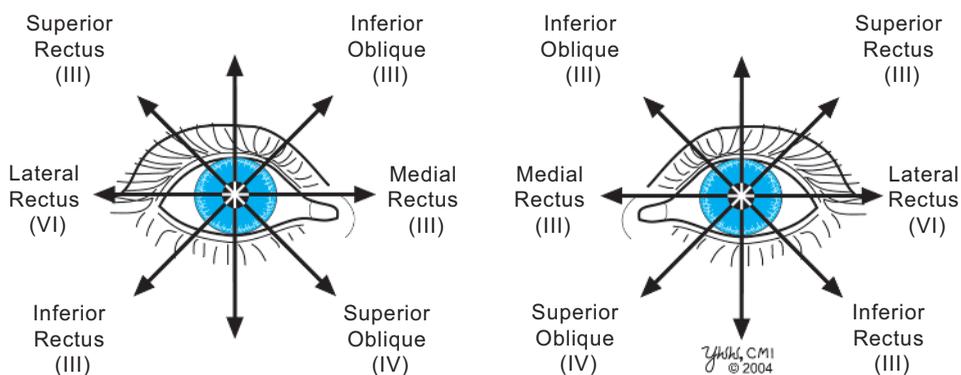
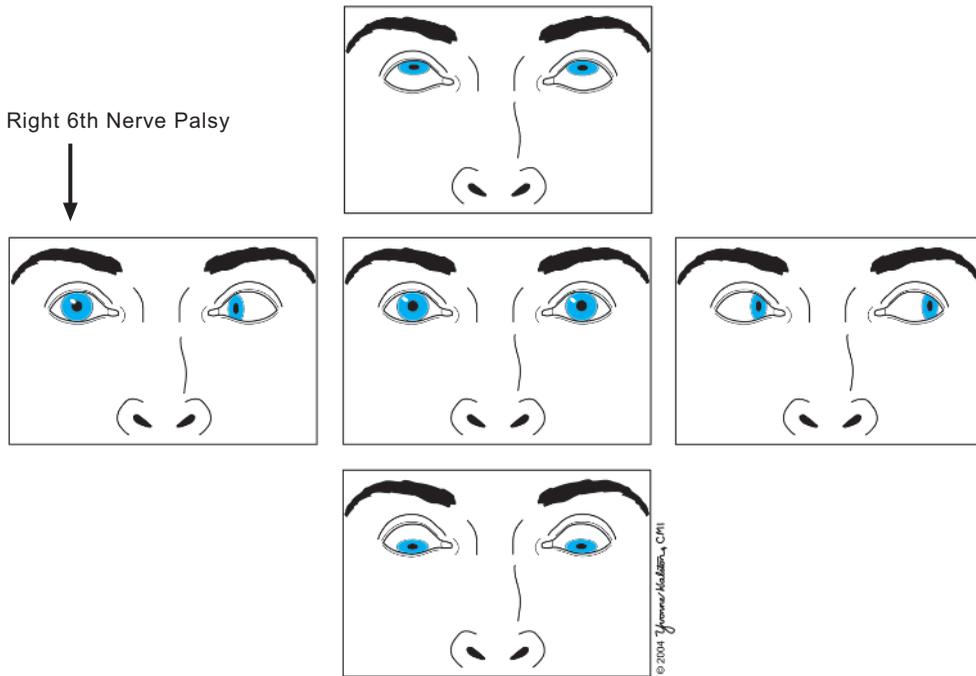


Figure 2-1 Directions of gaze.



**Figure 2-2** Right CN VI palsy. The right eye fails to abduct when the patient looks to the right.

movements are conjugate (eyes move together), move the entire range, and are smooth. Presence of double vision in one gaze direction suggests dysfunction of a given nerve or eye muscle. Figure 2-2 demonstrates a patient with a right CN VI palsy. Nystagmus often is normal when seen at end of horizontal eye movement but abnormal if present in near mid position.

The size of the palpebral fissure (distance between upper and lower eyelid) depends on CN III and sympathetic nerves. Marked drooping of the upper eyelid (ptosis) that interferes with vision implies CN III dysfunction or prior eye trauma. Mild ptosis without obstruction of vision implies sympathetic nerve dysfunction. When mild ptosis is combined with ipsilateral miosis, the lesion is called Horner's syndrome.

## CN V

*Trigeminal nerve* function is tested by evaluating face sensation. Lightly touch the three divisions of CN V with a cotton tip, your fingers, or a cool tuning fork. The patient should perceive these as equal

on both sides. The corneal reflex (touching the edge of the cornea over the outside of the iris with a wisp of cotton or a soft facial tissue) should produce prompt blinking of both eyes. Failure to blink in either eye suggests an afferent problem in the stimulated CN V, failure of the ipsilateral eye but not the contralateral eye to blink suggests dysfunction of ipsilateral CN VII, and failure of the contralateral eye to blink but not the ipsilateral eye suggests dysfunction of contralateral CN VII. Having the patient open his or her jaw and attempt to move the jaw laterally against resistance tests motor fibers of CN V.

## CN VII

*Facial nerve* function is evaluated by testing facial muscles. Ask the patient to open his or her eyes wide, close them shut tightly, and pull back his or her lips. The muscles of facial expression, innervated by CN VII, should show equal and symmetrical movement on both sides of the face.

A lower motor neuron lesion (facial nerve or nucleus) produces weakness of both the upper and

lower face. An upper motor neuron lesion (corticobulbar tract above the level of CN VII nucleus) causes weakness only of the lower face because forehead muscles receive bilateral innervation.

The chorda tympani nerve branch can be tested by determining whether the patient can detect the taste of sugar or salt placed on the anterior two thirds of one side of the tongue.

### CN VIII

*Auditory nerve* hearing evaluation is tested by masking the opposite ear with a finger or sounds and determining whether the patient can hear whispers (mid sound frequencies) or rubbing fingers (higher sound frequencies) in the other ear. If there is hearing loss, the external auditory canal should be inspected with an otoscope. Vestibular nerve testing is described in Chapter 21 “Disorders of the Vestibular System.”

### CN IX

*Glossopharyngeal nerve* function is tested by asking patient to say, “aah” and observing whether the soft palate and uvula rise symmetrically. Deviation of the uvula and soft palate to one side indicates a lesion on the contralateral nerve, unless the person has scarring from a prior tonsillectomy. One can also touch the pharynx with a cotton swab and observe for a gag reflex from CN IX and CN X.

### CN X

*Vagus nerve* function is tested by listening for hoarseness in the patient’s voice. If present, vocal cord movements can be visualized by otolaryngological methods to confirm paralysis.

### CN XI

*Accessory nerve* function is tested by shoulder shrug and head turn. Ask the patient to shrug his or her shoulders to the ears and then push down. Strength should be even. Then ask the patient to turn his or her head to either side while you apply resistance with your entire hand on the lower jaw. Again, strength should be even. Remember that the right sternocleidomastoid muscle turns the head to the left.

### CN XII

*Hypoglossal nerve* function is evaluated by asking the patient to protrude the tongue straight out and move it from side to side. Deviation of the tongue to one side with atrophy and fasciculations on that side of the tongue suggest an ipsilateral lower motor neuron lesion.

The patient should be able to smoothly flex his or her neck to touch the chin on the chest and rotate the head fully toward the shoulders. In meningitis, the patient cannot flex or resists flexing the neck, while in cervical arthritis, there is restricted rotation of the neck.

## Motor Examination

A complete motor examination involves evaluating muscle bulk, tone, strength, and gait, plus looking for involuntary movements. *Muscle bulk* compares the size of muscles on each side. In particular, observe the hands for atrophy of small intrinsic muscles and feet for atrophy of intrinsic foot muscles, seen by permanent elevation of toes at the second metatarsal joints (hammer toes). Atrophy from lower motor neuron lesions (denervation) shrinks a muscle by two thirds of its normal size. If the denervation is active, fasciculations are seen. Upper motor neuron lesions, disuse, or deconditioning reduces bulk by only one third, without fasciculations.

In evaluating *muscle tone*, the patient is asked to relax like a “rag doll” while you move the limbs through extension, flexion, and rotation. Think of tone as a rubber band and decide if the patient is floppy (hypotonic), normal, or too tight (exhibiting spasticity or rigidity). Hypotonia suggests a cerebellar or lower motor neuron lesion. Spasticity is increased tone similar to opening a pocketknife. The initial movement of the blade is hard, followed by an easy movement that fully opens the blade. Rigidity is resistance to limb movement that is consistent through the entire range (like bending a lead pipe), as seen in Parkinson’s disease.

*Muscle strength* is commonly evaluated using the British Medical Research Council method, where strength is graded on a relative scale of 0 to 5 (Table 2-2). In this relative system, the muscle strength of both a healthy grandmother and weight lifter would be 5. The value of this scoring

**Table 2-2 British Medical Research Council Method of Scoring Muscle Strength**

Score	Strength Finding
0	No movement
1	Flicker movements
2	Movement with gravity eliminated
3	Movement against gravity only
4	Full movement against some resistance
5	Full movement against full resistance

system is that it is highly reproducible between examiners. The disadvantage is that it is insensitive to slight worsening of mild weakness since both would be scored 4.

Since there are over 600 muscles in the human body, it is useful to group muscles into proximal and distal muscles (Table 2-3). It is helpful to ask the patient to flex or extend the limb and hold it there against the examiner’s force. Start with minimal pressure and then increase until maximal or the limb gives way. True weakness tends to be gradually overcome as the examiner pressure

increases. Giving way or suddenly letting go of a position by a patient may indicate pain in a limb or reluctance to give “full effort.”

Weakness comes from many anatomic locations. Figure 2-3 shows the key anatomy of the corticospinal tract, which produces upper motor neuron lesions. Later chapters on the approach to the patient (Chapter 1) and disorders of muscle (Chapter 4), neuromuscular junction (Chapter 5), peripheral nerve (Chapter 6), spinal cord (Chapter 7), brainstem (Chapter 8), and cerebrovascular disease (Chapter 9) provide additional ways to evaluate the motor system.

*Gait* evaluation is the most useful screening test of the motor system. Ask the patient to get out of the chair and walk normally, then on toes and heels, and turn. One can also ask the patient to hop or walk backward. Observe for smoothness of gait, attitude of the trunk and arms, steadiness during turns, appropriate arm swings, and balance. The presence of an asymmetrical gait or limp may reflect a hemiparesis, leg joint arthritis, old fractures, balance problems, or leg pain that must be sorted out.

Balance can be evaluated by using the Romberg position and tandem gait. In the Romberg test, the individual is asked to put the feet together and balance

**Table 2-3 Muscles Commonly Tested and Their Nerve Root and Peripheral Nerve**

Limb	Muscle (Function)	Nerve Root	Peripheral Nerve
<i>Arm Proximal</i>	Deltoid (shoulder adduction)	C5	Axillary
	Biceps (elbow flexion)	C5	Musculocutaneous
	Triceps (elbow extension)	C7	Radial
<i>Distal</i>	Flexor carpi radialis and ulnaris (flexion wrist)	C6-7	Median and ulnar
	Extensor carpi radialis and ulnaris (extension wrist)	C6-8	Radial
	Abductor pollicis brevis (thumb abduction)	C8	Median
	Abductor digiti minimi (little finger abduction)	T1	Ulnar
<i>Leg Proximal</i>	Iliopsoas (hip flexion)	L2-4	Femoral
	Quadriceps (knee extension)	L2-4	Femoral
	Hamstrings (Knee flexion)	L4-S1	Sciatic
<i>Distal</i>	Tibialis anterior (ankle dorsiflexion)	L4-5	Peroneal
	Gastrocnemius (ankle flexion)	S1-2	Tibial
	Tibialis posterior (ankle inversion)	L5	Tibial
	Extensor hallucis longus (great toe dorsiflexion)	L5-S1	Peroneal
	Foot flexors (dorsiflexion of all toes)	L5-S1	Tibial

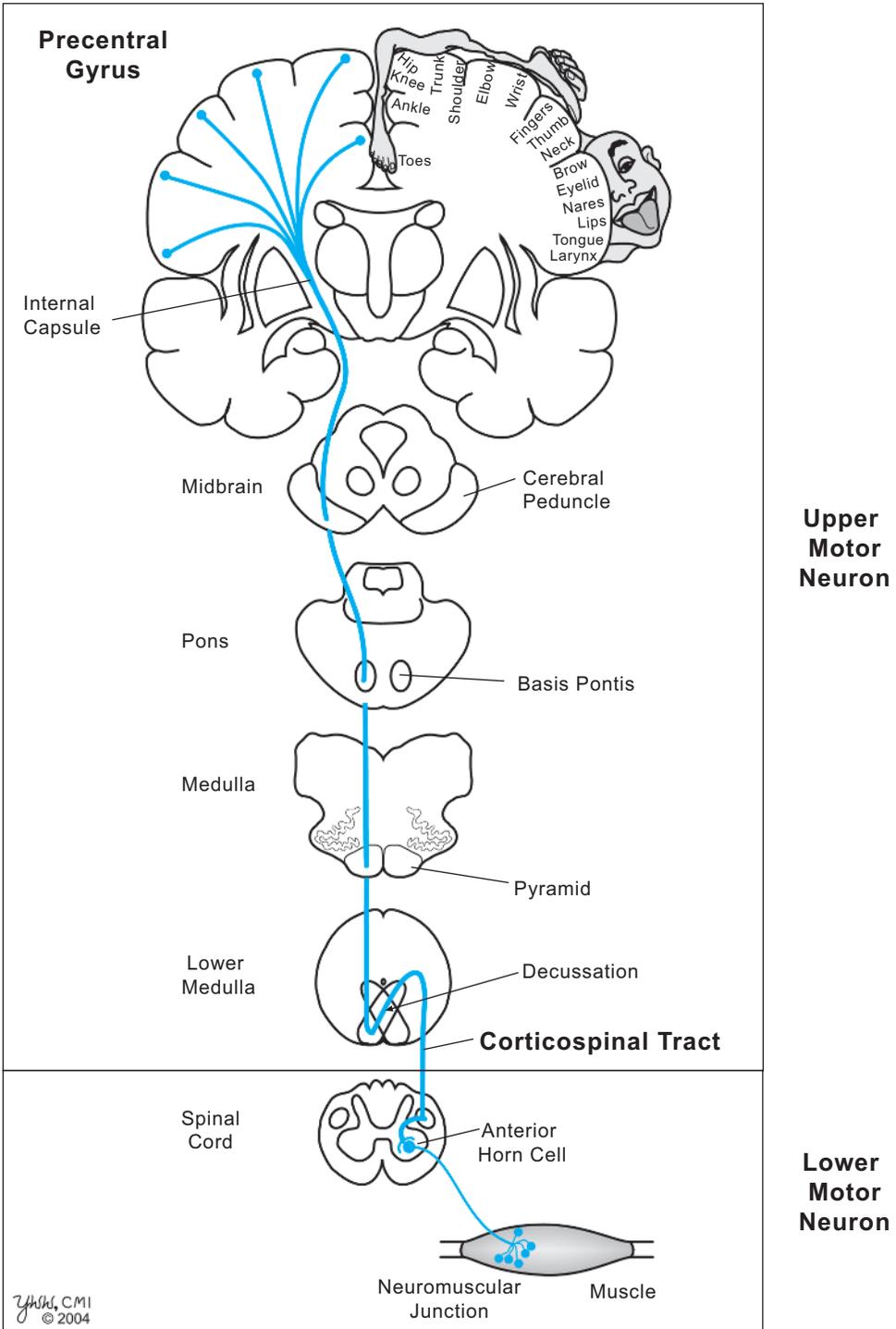


Figure 2-3 Anatomy of the corticospinal tract.

with the eyes open. If the balance is normal, the patient is asked to close the eyes, thus assuming the Romberg position. Marked sway or loss of balance with eyes closed, but not when open, is the Romberg sign. This sign is usually due to poor position sense in the feet. In tandem walking, the patient attempts to walk heel to toe in a straight line. Abnormal tandem gait implies dysfunction of inner ear, position sensors in the feet, vestibular brainstem or cerebellar nuclei or tracts, or orthopedic leg problems.

Involuntary movements should be noticed during the history and exam and most commonly involve the arms. In general, the movements should be evaluated to determine whether they (1) are unilateral or bilateral, (2) involve arms, legs, or the head, (3) are continuous or intermittent, (4) occur at rest, during static position of the limb, or during purposeful movements, and (5) can voluntarily be abolished. Types of involuntary movements include tremor, dystonia, chorea, ballismus, tics, and myoclonus. Most involuntary movements are due to disorders of the basal ganglia. Chapter 12 “Disorders of the Extrapyrarnidal System” describes these involuntary movements.

## Coordination

For coordination to be tested, the patient must have normal or near-normal muscle strength in their limbs. The finger–nose–finger test asks the patient to touch the tip of the index finger to the nose, then to the examiner’s finger, and back to the nose again. Cerebellar dysfunction causes a tremor perpendicular to the direction of movement that intensifies as the finger nears the target. The heel–to–shin test asks the patient to place a heel on the opposite knee with the ankle dorsiflexed and then slide the heel down the front of the shin to the great toe. Again cerebellar dysfunction causes the heel to move perpendicular to the line of heel movement. The rapid alternating movement test asks the patient to pat the knee with the palm and then the back of the hand as he or she gradually increases the speed.

## Sensation

The evaluation of sensation is often divided into small nerve fiber peripheral nerve functions (pain and temperature), large nerve fiber peripheral nerve functions (vibration, position sense, and

touch), and cortical sensory functions (stereognosis, graphesthesia, and two-point discrimination). Normally, the tests are performed on the hands and feet unless the history or exam suggests damage to particular nerves or roots (Figures 2-4a and 2-4b).

*Pain* is usually tested with a new safety pin; the patient is asked to determine whether the gentle prick was “sharp” from the pin edge or “dull” from clip edge. One compares the sides and other areas of the limb. Always discard the safety pin when finished.

*Temperature* is usually tested with a cool metal object such as a tuning fork. The control temperature for comparison is the face or upper arm. The patient is asked whether the test skin area is as cool as the control skin area. The test is usually done on the dorsum of the foot and moves up the leg until the temperature is perceived as cool.

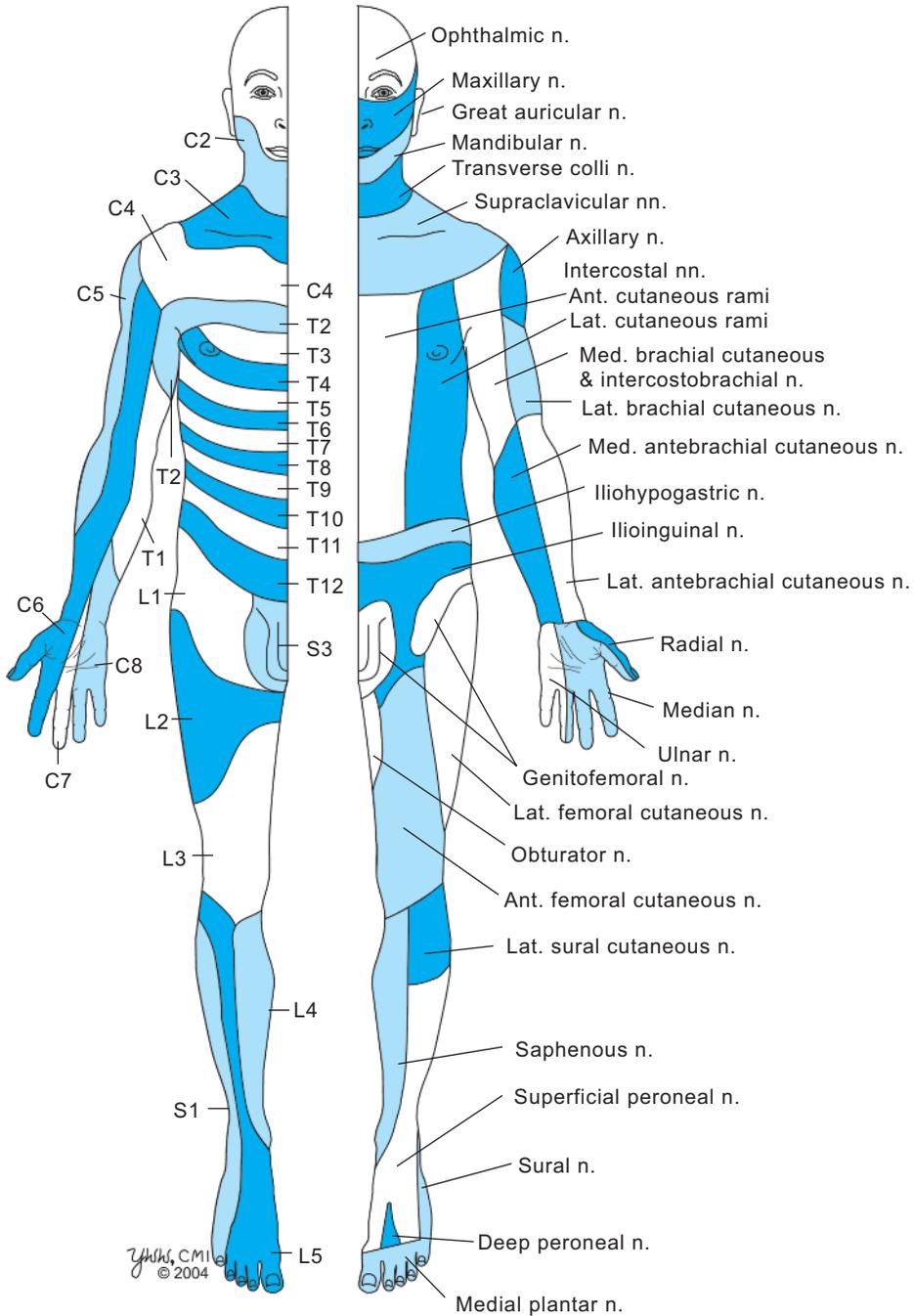
*Vibration* is tested with a 128-Hz tuning fork by pressing the stem over the great toe and placing your finger beneath the toe. The patient is asked to say when the vibration disappears, which should be when the clinician can no longer feel it vibrate in his or her finger. The tuning fork is moved up the leg proximally until the patient perceives the vibration well. If the toes have normal vibration sensation, testing the fingers is seldom necessary.

*Position sense* is determined by grasping the great toe on the sides and instructing the patient to respond “up” or “down” from where the toe was last time. Move the toe only a millimeter or two. If the patient has trouble distinguishing up or down, one can move the toe in a larger arc until satisfied that the patient can detect movement. If the toes are normal, testing the fingers is seldom necessary.

*Touch* evaluation comprises two tests. Stereognosis is tested with the eyes closed and asking the patient to identify simple objects placed in the hand, such as coins or a key. Graphesthesia is tested with the eyes closed and asking the patient to identify numbers or letters written on the palm of each hand. These tests require normal primary sensation and abnormalities imply dysfunction in the contralateral sensory cortex or parietal lobe (see Chapter 11 “Disorders of Higher Cortical Function”).

## Reflexes

Deep tendon reflexes (DTRs), or stretch reflexes, evaluate a local circuit from muscle spindles to



**Figure 2-4** Dermatomes and peripheral nerve distributions. (a) Anterior view. (Continues)

spinal cord level and back to the appropriate muscles. The most common reflexes tested are biceps jerk (BJ), triceps jerk (TJ), knee jerk (KJ), and ankle jerk (AJ) (Figure 2-5). Position the patient comfortably, usually with the arms resting on the thighs and

the feet just touching the exam step or the floor. Using a long, well-balanced hammer with a soft percussion tip, tap the tendon to deliver the stimulus. The key is to be consistent in the application of force. If the reflex is difficult to attain, it can be aug-

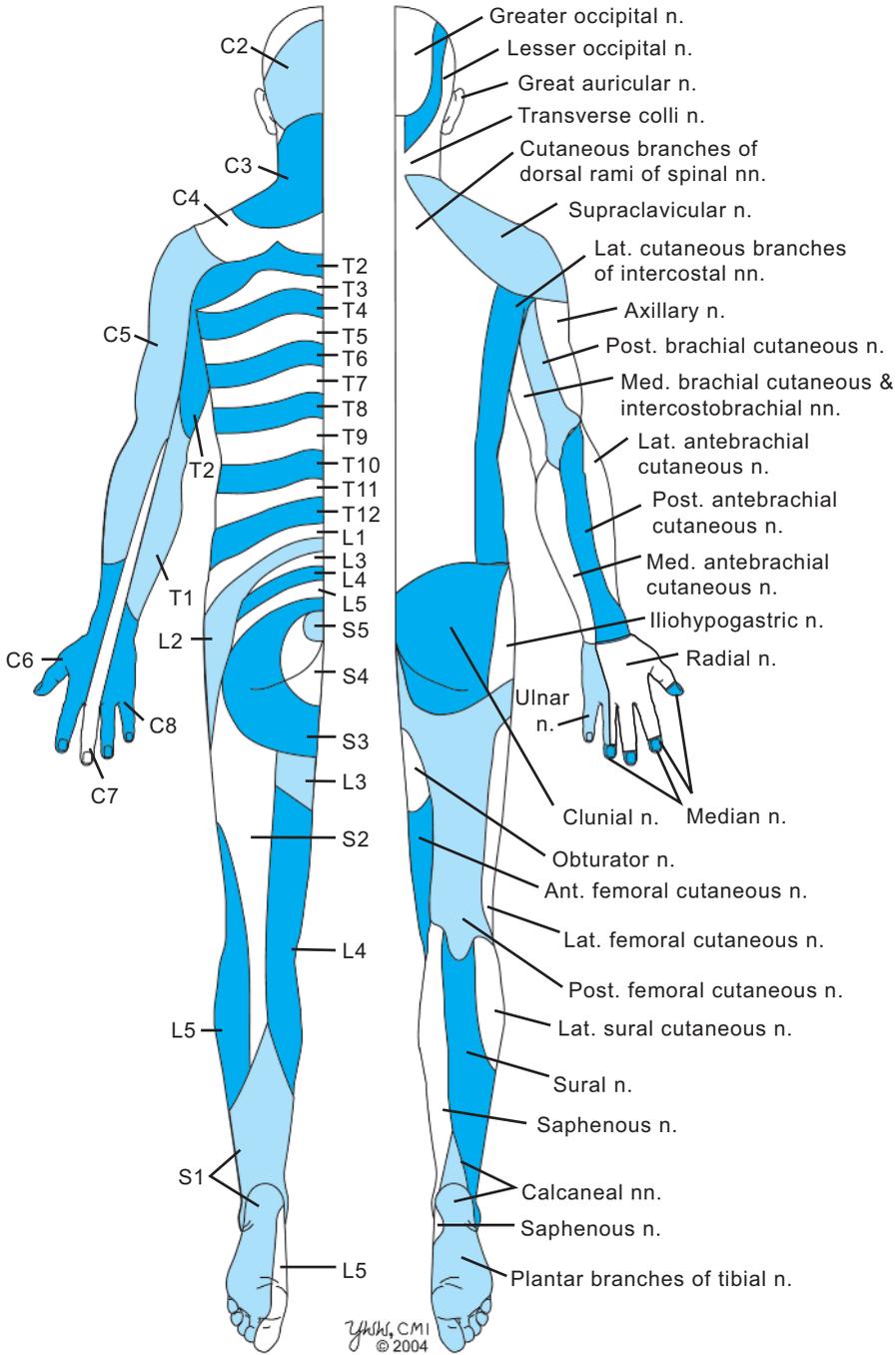


Figure 2-4 (b) Posterior view. (Continued)

mented by asking the patient to grit his or her teeth or make a fist with the other hand. Children and young adults, especially if anxious or cold, tend to have brisk reflexes, while the elderly often have diminished reflexes. DTRs are scored per Table 2-4.

The extensor plantar reflex or Babinski sign suggests damage to the corticospinal tract (upper motor lesion) in children older than 2 years and adults. It is elicited by scratching the sole of the foot (usually with a key) from the heel, along the

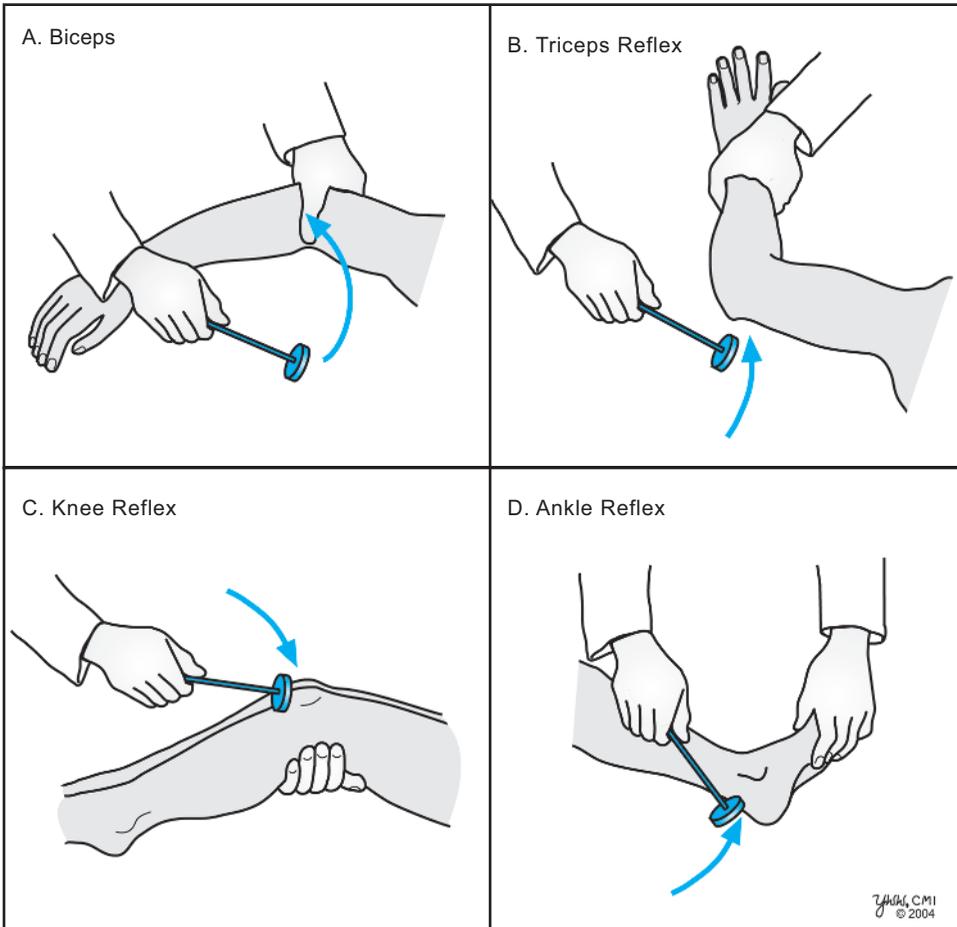


Figure 2-5 Deep tendon reflexes.

lateral aspect of the foot, and finally arching across the ball of the foot to the great toe. The Babinski sign is present if the great toe extends with fanning of the other toes. A Babinski sign is stereotypical and similar each time you perform the maneuver.

Table 2-4 Scoring Deep Tendon Reflexes

Score	Reflex Finding
0	Absent
1+	Diminished, often requiring reinforcement
2+	Normal or physiologic
3+	Normal for age and brisk without clonus
4+	Abnormally brisk, usually with clonus

Withdrawal from “tickling” tends to be erratic, does not look the same way each time, and is often triggered by touching the sole of the foot anywhere.

Frontal lobe release signs imply bilateral frontal lobe damage. The grasp reflex is elicited by nonvoluntarily persistent grasping of the examiner’s fingers when placed or lightly stroked across the patient’s palm. Other frontal lobe release signs are discussed in the Chapter 11 “Disorders of Higher Cortical Function.”

## Pediatric Neurologic Exam

The most striking difference in the pediatric and adult neurologic exams is that the age of the patient requires very different exam techniques and elements. The key portions of the exam are

testing the same systems, albeit in different ways. As a child gets older, the clinician can incorporate more and more of the adult exam into the pediatric exam. Therefore, the infant exam will be presented, as it is the most disparate of the pediatric stages as compared with the adult.

## General

Observe the baby. How does he or she act? Is the patient irritable, easily consoled, sleeping and easy to arouse, or somnolent? Encephalopathy in the infant often presents as hyperirritability. Do the face or other features appear dysmorphic? Note the set of the eyes and ears.

## Skin

Always get the clothes off the infant. Look for hyper- or hypopigmentation. Check the base of the spine for dimpling or hair tufts. Examine the diaper area; note the morphology of the genitalia.

## Head

Always measure head circumference. This should be compared with all previously obtained measures if possible. The parents can be measured as well. Large-headed parents can produce large-headed children.

The anterior fontanel should be soft, not tense or sunken. Some pulsation is normal. The posterior fontanel should not be palpable after birth.

## Eyes

Check eye movements by giving the child something to observe. In infants, faces work well at a distance of about 6 inches. In older babies, round, red objects can catch their attention. Check for smooth movements and the extent of tracking. Tracking past midline begins around age 2 months. Vertical tracking begins around 3 to 4 months.

Fundoscopic exam is important to identify the red reflex. To do this, while looking through the ophthalmoscope, aim at the child's eye. If the red of the retina can be seen, there is a red reflex. This screens for congenital cataracts and retinoblastoma. If the infant is cooperative, the clinician may actually be able to examine the back of the eye.

Also using the ophthalmoscope or a penlight, check for the pupillary light response.

## Mouth

Using a gloved little finger, check for the suck reflex. Infants should latch on and the examiner's finger should not slip from the mouth during suck. While this finger is in the infant's mouth, also check for palate height. At some point during the exam, the baby will probably cry. Use this opportunity to assess palate elevation.

## Tone

Always assess tone when the head is midline. When the head is turned, this triggers the asymmetric tonic neck reflex (*fencer posture*), producing increased tone on the side opposite the head turn. Passively move the arms and legs. The child should move somewhat in response and not be totally limp. The examiner should pick up the baby, with hands around the infant's chest. Does the baby slip through the fingers or stay between the hands without holding onto the chest? The former demonstrates hypotonia. Hypertonia is evident when the child's legs scissor when vertically suspended. For further tone assessment, turn the baby on his or her belly with a hand and support the stomach and chest. Does the patient flop over your hand, arch the back and neck slightly or stay rigidly extended? These are signs of hypotonia, normal tone, and hypertonia, respectively. Now place the infant on its back. A normal posture in the infant is flexion of all four extremities. As a baby gets older, the limbs assume a more extended posture. Take the baby's hands and pull to a seated position. Resist the urge to support the head. Even at birth, the full-term infant will flex the extremities and pull the head up.

## Reflexes

Always assess reflexes when the head is midline for the same reasons as above. Check the deep tendon reflexes as in the adult; however, these can usually be tapped with the fingers in infants. Ankle clonus is usually present in infants. Three to four beats bilaterally are normal. Sustained clonus or asymmetries should be noted.

## Primitive Reflexes

After checking for the suck reflex, one should also check Moro, grasp, and step reflexes.

### MORO

With the infant on his or her back, grab the hands, lift the baby slightly off the bed, and then allow to drop back onto the bed. The response should be a symmetric brisk extension of arms and legs and then drawing of the arms back to midline.

### GRASP

Place a finger into the baby's palm. The infant should firmly grasp it, equally on both sides.

### STEP

Lift the infant to standing position on the examining surface (with the examiner supporting the weight). The baby should take automatic steps on the table or bed.

### ROOT

Brush the side of the child's cheek. The head will turn toward the cheek touched.

Table 2-5 shows the timing of appearance and disappearance of these primitive reflexes. Always remember to re-dress and swaddle the baby after finishing.

**Table 2-5 Primitive Reflexes with Expected Time of Appearance and Disappearance**

Reflex	Appears by (Gestation Period)	Gone by (Approximate)
Suck	34 wk	4 mo
Root	34 wk	4 mo
Palmar Grasp	34 wk	6 mo
Plantar Grasp	34 wk	10 mo
Tonic Neck	34 wk	4–6 mo
Moro	34 wk	3–6 mo
Automatic Step	35 wk	2 mo

## RECOMMENDED READING

British Medical Research Council. *Aids to the Examination of the Peripheral Nervous System*. 4th ed. Philadelphia: W. B. Saunders; 2000. (*Superb booklet that outlines how to test each muscle, describes areas of sensation for all peripheral nerves, and easily can be kept in doctor's bag.*)

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## 3 COMMON NEUROLOGIC TESTS

### Overview

Neurologic tests serve to (1) establish a diagnosis when several possible diagnoses exist, (2) help clinicians make therapeutic decisions, and (3) aid in following the results of treatment. In broad terms, neurologic tests can be divided into those that evaluate function, structure, and molecular/genetic concerns. For example, the neurologic examination is the most exquisite test of neurologic function yet devised. While it will provide clues as to the general location of the disease process, it is less reliable than other tests. Cranial magnetic resonance imaging (MRI) and computed tomography (CT) precisely locate abnormal brain tissue but cannot decipher the physiologic consequences of the tissue abnormality.

In this chapter, the major neurologic tests are briefly discussed in terms of their basic principles, indications, cost, and side effects.

### Functional Neurologic Tests

#### Neurologic Examination

This test is the entry point into the diagnostic and therapeutic process. The history and neurologic examination yield information about normal and

abnormal neurologic functioning of the patient. The neurologic exam also gives information about the general anatomic location of the disease and the likely type of disease process. In some diseases (e.g., migraine headache, trigeminal neuralgia, schizophrenia) the neurologic history and exam is the only test that yields the diagnosis. For optimal results, this test requires the patient to be alert, cooperative, and not aphasic or demented. The test is safe, inexpensive, comfortable, and can be repeated frequently. A complete history and physical exam requires 30 minutes to 1 hour (see Chapter 2, “Neurologic Examination”).

#### Neuropsychologic Tests

Neuropsychologic tests evaluate higher cortical function and do so with a higher degree of precision and certainty than usual bedside testing. A certified clinical neuropsychologist usually administers these tests. A variety of tests have been developed and standardized to enable better evaluation of different aspects of cortical function (Table 3-1). While neuropsychologic tests are sensitive indicators of a cognitive disorder, they do not highly localize the part of the cerebral cortex that is dysfunctional. Although the tests are quantitative, the score does not highly correlate with size of a lesion.

**Table 3-1 Neuropsychologic Tests and Functions Evaluated**

Test	Function Best Evaluated
Weschler Adult Intelligence Scale-III and Weschler Intelligence Scale for Children-III	Intelligence
Weschler Memory Scale	Frontal lobe
Milan Sorting Test	Frontal lobe
Porteus Maize Test	Frontal lobe
Weschler Block Design	Parietal lobe
Benton Figure Copying Test	Parietal lobe
Halstead-Reitan Battery (parts)	Temporal lobe
Milner's Maze Learning Task	Temporal lobe
Minnesota Multiphasic Personality inventory	Personality
Rorschach Test	Personality

These tests are used to (1) divide cognitive abnormalities into specific subtypes that may assist in establishing a diagnosis, (2) determine a quantitative score on specific tests so that repeated tests can measure disease progression or improvement, (3) distinguish dementia from psychologic illnesses such as depression, and (4) determine an intelligence quotient (IQ) score for legal or medicosocial reasons. For the usual patient with marked dementia from Alzheimer's disease, neuropsychologic tests add little. One should clearly state the reason for ordering the testing so the neuropsychologist can construct the most useful battery of tests to give the patient.

Neuropsychologic tests are safe, inexpensive, and comfortable to the patient. Testing takes 1 to 4 hours depending on the extent of the battery. These tests can be repeated occasionally but cannot be administered frequently as repeated testing at short intervals would produce a "learning effect" that could falsely improve the score.

### Electroencephalogram (EEG)

The EEG is a tracing of electronically amplified and summated electrical activity of the superficial layers of the cerebral cortex adjacent to the calvarium. This electrical activity comes primarily from

inhibitory and excitatory postsynaptic potentials of pyramidal cells. Electrodes are placed over the scalp in precise locations to record the brain's electrical activity when awake and often during sleep. Differences in voltage between 2 selected electrodes plotted over time are produced as continuous digital waveforms on a computer monitor or as similar analog waveforms on long sheets of paper. The complete EEG tracing is made up of waveforms from several different source electrodes. A trained technician performs the EEG and a neurologist interprets the tracing.

Information derived from an EEG is divided into waveforms that suggest epileptiform brain activity and those that suggest an encephalopathy (metabolic or structural in origin). Epileptiform brain waves (spikes and sharp waves) are paroxysmal, repetitive, brief, and often of higher voltage than background activity. Background activity is divided into 4 different frequencies (in Hz):  $\beta$  (>12 Hz),  $\alpha$  (8–12 Hz),  $\theta$  (4–7 Hz), and  $\delta$  (0–3 Hz) that range from fast to slow. The  $\alpha$  frequency is the dominant EEG frequency seen in occipital leads when an awake individual has his or her eyes closed.

Most encephalopathies produce slowing of background activity, often into the  $\delta$  range. EEG electrical activity only comes from intact responding neuronal populations and does not emanate from brain tumors or dead neurons in infarcted brain. However, localized brain masses (tumor or abscess) produce a localized slowing ( $\delta$  waves) from dysfunctional neurons located around the mass. Some drugs (especially barbiturates) increase background activity into the  $\beta$  range.

While an EEG gives considerable information about abnormal brain function, it provides limited information as to the precise location of the brain dysfunction. Since electrical currents flow by a path of least resistance, the actual source of the electrical activity may not be directly beneath the recording electrode. In general, conventional methods localize the EEG source to a 2-cm cube. Under some circumstances, the EEG is coupled with a video monitor so the patient's behavior can be correlated with EEG findings. The EEG is often performed during wakefulness and sleeping as epileptiform discharges are usually more frequent during sleep. The EEG can also study patients during sleep to evaluate sleep abnormalities, such as narcolepsy. Under special circumstances, electrodes can be surgically placed over the cortical

surface or within the brain to search for specific foci of seizure genesis.

With the advances in CT and MRI, indications for ordering an EEG have diminished. Present indications for ordering a routine EEG include (1) evaluating unwitnessed episodes of loss of consciousness for likelihood of seizures, (2) characterizing interictal (between seizures) brain activity to better determine the type of seizure disorder, (3) distinguishing encephalopathy from frequent seizures (status epilepticus) in a stuporous or comatose patient, (4) distinguishing nonepileptic events from true seizures, and (5) determining brain death.

The routine EEG is safe, inexpensive, and comfortable to the patient and takes about 2 hours to complete. An EEG can be repeated as often as necessary. Figure 3-1 demonstrates typical EEG changes.

### Electromyogram (EMG)

The EMG is the evaluation of the electrical function of individual muscle motor unit potentials at rest and during muscle contraction. It is performed by inserting a recording needle electrode into the belly of a muscle. The needle tip is the recording electrode and the needle shaft is the reference electrode in a

concentric needle while a monopolar needle compares the fibers' electrical signal with that of a reference electrode on the skin surface. Electrical activity from muscle fibers is recorded and amplified to appear on an oscilloscope as a tracing of voltages versus time with accompanying sound. Physicians need special training to perform the EMG.

Abnormal motor units or individual muscle fibers demonstrate changes in duration, amplitude, and pattern of the waveform that occur during needle insertion, rest, or voluntary contraction. An EMG distinguishes normal muscle from disease due to nerve damage or muscle disease. An EMG is safe, somewhat uncomfortable to the patient, inexpensive, and requires 30 to 60 minutes. To minimize patient discomfort, the patient should receive a clear description of what will happen and frequent reassurance. The following is a description of the types of findings seen on EMG.

#### NORMAL MUSCLE

Insertion of a needle into a normal muscle injures and mechanically stimulates many muscle fibers, producing a burst of action potentials of short duration (<300 msec). At rest, normal muscle is electrically silent as normal muscle tone is not the

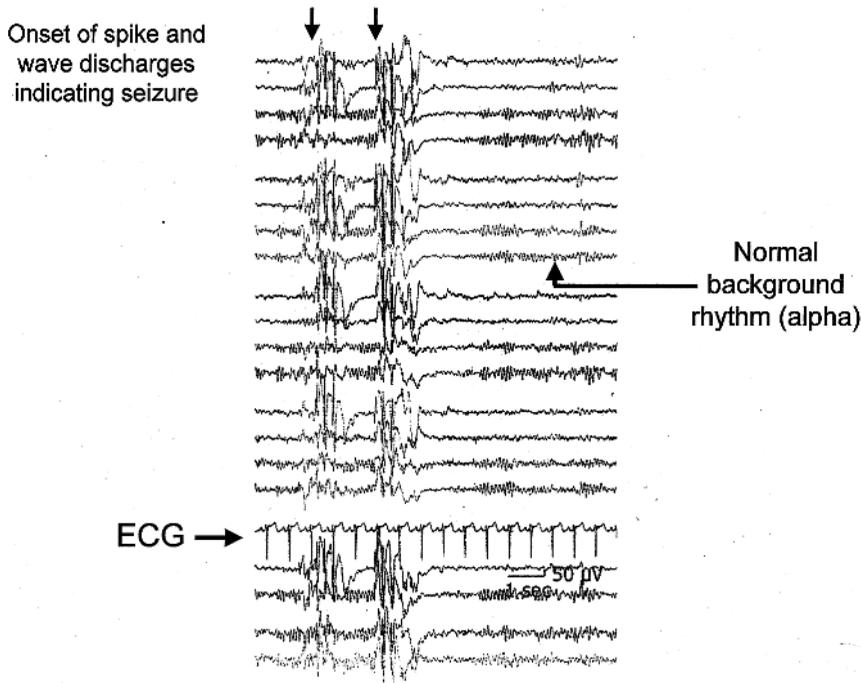


Figure 3-1 Electroencephalogram typical of seizure.

result of electrical contraction of muscle fibers. As an electrical impulse travels along the surface of a single muscle fiber toward the recording electrode, the impulse becomes positive (downward deflection by convention) relative to the reference electrode. As the impulse comes beneath the electrode, the waveform becomes negative (upward deflection) and then becomes slightly positive and returns to baseline as the impulse travels past the electrode (Figure 3-2). A single muscle fiber contraction lasts about 2 to 4 milliseconds and is less than 300  $\mu\text{V}$  in amplitude. The firing of a single muscle fiber (called fibrillation, which does not cause visible muscle movement) does not occur normally and is a sign of muscle membrane instability either from denervation or myopathy. In normal muscle, an electrical impulse travels from a spinal cord anterior horn neuron (lower motor neuron) along its axon to eventually innervate 10 to 1,000 muscle fibers (called a motor unit). The number of muscle fibers innervated depends on the muscle, with proximal limb muscles having the highest number of innervated muscle fibers. During mild voluntary muscle contraction, an entire motor unit fires almost simultaneously, producing a motor unit action potential (MUAP). A typical MUAP has 3 to 4 excursions across the baseline

(phases) and a maximum amplitude of 0.5 to 5 mV (Figure 3-2). The shape and duration of a given MUAP remain quite constant on repeat firings and generally appear different from other nearby MUAPs.

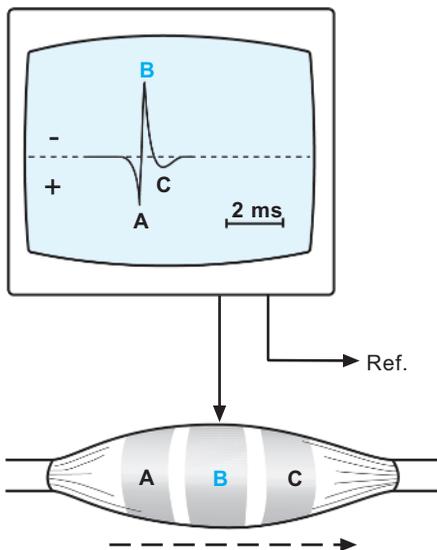
#### DENERVATED MUSCLE

Immediately after complete nerve transection, the muscle is paralyzed, unexcitable by nerve stimulation, and electrically silent by EMG except for insertion potentials. Beginning 2 to 3 weeks after a muscle loses its innervation, spontaneous individual muscle fiber contractions may appear. The EMG demonstrates fibrillations and positive sharp waves (brief monophasic positive spikes). Until the motor unit completely degenerates, spontaneous firing of the MUAP (fasciculation, which produces a visible muscle twitch) also occurs. If the nerve damage is incomplete and occurred several months earlier, the denervated muscle fiber induces adjacent motor nerves to branch or sprout and send a nerve branch to reinnervate the denervated muscle fiber (called “sprouting”). MUAPs suggestive of sprouting are of longer duration, contain more phases, and may be of higher maximum amplitude than normal (Figure 3-3c).

#### MYOPATHY

Death or dysfunction of scattered muscle fibers results in MUAPs during voluntary muscle contraction that are of shorter duration and lower amplitude than normal (Figure 3-3b). Some MUAPs may be polyphasic from loss of synchronous firing. In myositis, there may be accompanying fibrillations due to inflammatory damage to adjacent motor nerve endings.

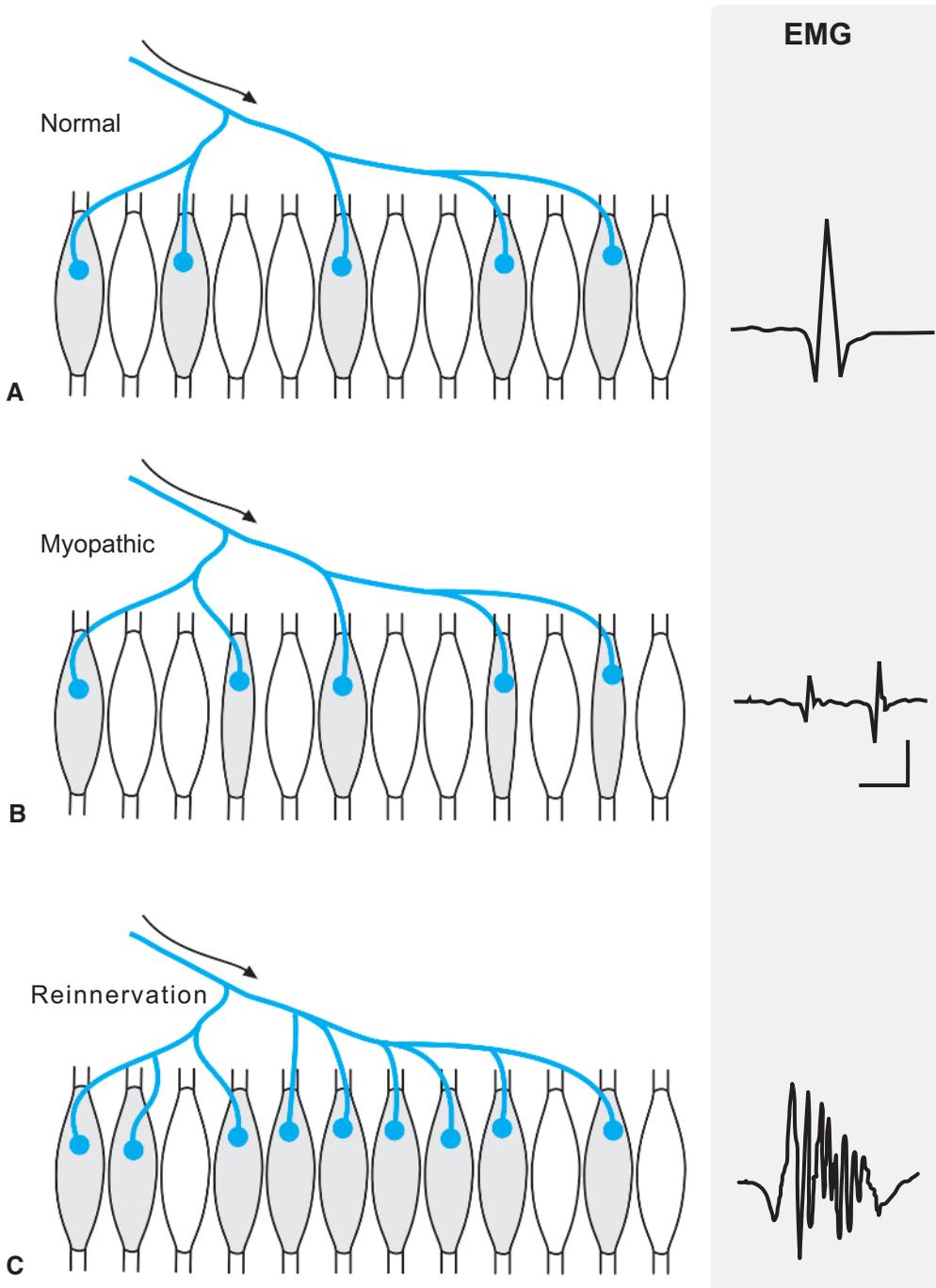
In myopathies that cause myotonia (such as myotonic dystrophy), insertion of the needle produces a train of high-frequency repetitive discharges in a positive sharp waveform that diminish in frequency and amplitude over a few seconds. When heard over a speaker, myotonic discharges sound like a “dive-bomber.”



**Figure 3-2** Electromyogram recording of a single muscle fiber with electrical activity following the dashed arrow.

#### Nerve Conduction and Neuromuscular Junction Studies

Nerve conduction studies are undertaken to evaluate the functioning of motor, autonomic, and sensory nerves and neuromuscular junctions. It is



**Figure 3-3** Electromyogram (EMG) of motor units in disease.

possible to determine actual conduction velocities for nerves in the peripheral nervous system, but conduction velocities cannot be determined in the central nervous system. In the CNS, only a nerve

latency time can be obtained because the CNS nerves cannot be stimulated at various points along the nerve pathway. The test is performed by a physician with special training or by a skilled

technician under a physician’s supervision. The test is safe, inexpensive, mildly uncomfortable for the patient, and takes 1/2 to 1 hour.

Indications for ordering nerve studies include (1) determining whether a neuropathy is generalized or multifocal, (2) determining whether a neuropathy is mainly from demyelination or axonal loss, (3) localizing the site of a nerve conduction blockade, and (4) determining and characterizing neuromuscular junction abnormalities. In the common types of distal sensorimotor peripheral neuropathy, nerve studies seldom help establish the etiology.

**MOTOR NERVE FUNCTION**

Motor nerve conduction velocity studies measure the velocity of the fastest motor nerve axons at various points along a peripheral nerve. Peripheral nerves can be stimulated to fire by application of an electrical impulse to the skin overlying the nerve. When a muscle contracts, its electrical signal can be detected by placing an electrode on the skin above the muscle belly. The muscle electrical signal is recorded and the time from electrical stimulus to muscle contraction (latency) can be determined and displayed on an oscilloscope. A motor nerve velocity is determined as follows (Figure 3-4). By

moving the stimulating electrode along the nerve pathway, differing latencies (in milliseconds) to muscle contraction are determined. By measuring the distance along the nerve pathway between two exciting stimuli, one can divide the nerve distance (in mm) by the latency difference (in milliseconds) to obtain the nerve velocity (in m/s). Normal motor velocity of the median and ulnar nerves is 50 to 60 m/s and 40–50 m/s in the sciatic nerve. Slowing of the motor nerve velocity may reflect loss of myelin along the nerve (often causing slowing of velocities to 20 to 30 m/s) or loss of the fastest motor nerves (lesser degree of velocity slowing). Slowing of a motor nerve may occur along the entire nerve pathway or at a localized point of nerve compression, such as the ulnar nerve at the elbow.

**SENSORY NERVE FUNCTION**

Evaluating sensory nerve function is more difficult as the normal signals are weaker and more diffuse following an electrical stimulus because the conduction velocities of different sensory axons vary considerably. Sensory nerves may be unmyelinated and conduct at 1/2 to 2 m/s or be thinly myelinated and conduct at 10 to 20 m/s. The most common sensory nerve test determines the latency time from surface electrical stimulation of the interdigital

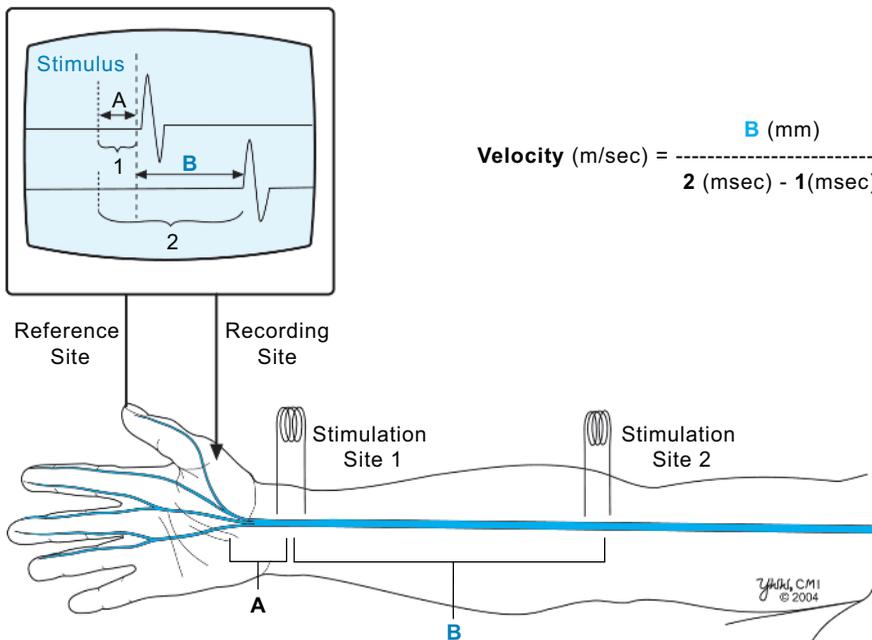


Figure 3-4 Motor nerve conduction velocity.

branch of the median nerve to a skin surface electrode site over the median nerve just proximal to the wrist. A delayed median nerve sensory latency suggests compression of the nerve at the carpal tunnel.

#### NEUROMUSCULAR JUNCTION FUNCTION

Information about the function of the neuromuscular junction can be obtained from repetitive nerve stimulation studies. Placement of a skin recording electrode over the belly of a muscle and stimulating the motor nerve produces a compound muscle action potential (CMAP). If the nerve stimulation is repeated, the CMAPs appear identical on the oscilloscope. In diseases of the neuromuscular junction, the amplitude of the CMAPs may decrease or increase. In myasthenia gravis and botulism, repetitive nerve stimulation produces a decremental response in the CMAP. The test is safe, inexpensive, somewhat uncomfortable, and takes about 15 minutes.

#### SENSORY EVOKED POTENTIALS

Occasionally there are indications to evaluate the integrity of central conduction along major sensory pathways (visual, auditory, and peripheral sensory system); these are called evoked potentials. As noted above, actual conduction velocities cannot be obtained, but central modality-specific latencies can. Evoked potential tests record computer averages of the EEG that are time locked to repeated (100–500 trials) specific sensory stimuli such as sound, light, or electrical stimulation of the peripheral nerve. The computer averaging reduces background EEG electrical activity to 0 while enhancing the time-locked stimulus signal. Abnormalities are characterized by a delay for the time-locked signal average to reach its destination or distortions (usually a prolongation of the waveform and loss of signal amplitude). Sensory evoked potentials are safe, inexpensive, and comfortable. The major indication is the evaluation of possible diseases that cause central nervous system (CNS) demyelination of these sensory pathways.

## Structural Neurologic Tests

### Lumbar Puncture (LP) and Cerebrospinal Fluid (CSF) Examination

Five important reasons for examining CSF are to (1) diagnose infections of the meninges, (2) diag-

nose cancer involving the meninges, (3) diagnose herpes simplex encephalitis and other encephalitis, (4) diagnose a small subarachnoid hemorrhage, and (5) introduce medications into the subarachnoid space or contrast media for a myelogram. In addition, there are several diseases where CSF examination helps make a specific diagnosis. These diseases include multiple sclerosis, Guillain-Barré syndrome, and paraneoplastic syndromes. The LP is not limited to establishing diagnoses. Antimicrobial and anticancer drugs can be delivered intrathecally into the lumbar or cisternal CSF to treat patients with some forms of infectious meningitis or meningeal carcinomatosis. The LP is safe, mildly uncomfortable, moderately expensive depending on tests ordered, and takes up to 1 hour.

#### CONTRAINDICATIONS FOR LP

There are times when it is not safe to perform an LP. If the individual has a localized mass in the brain or meninges or obstructive hydrocephalus that is creating marked increased intracranial pressure, removal of CSF from the lumbar space will lower the CSF pressure below the foramen magnum. This in turn may allow the brain to move through the tentorium (uncal herniation or tentorial herniation) or force cerebellar tonsils into the foramen magnum. To minimize this risk, a complete history and neurologic examination should always be done before the LP. If the patient has signs of marked increased intracranial pressure (papilledema), focal neurologic signs (especially hemiparesis, aphasia, or ataxia), or is comatose, elderly, or immunocompromised, it is usually advisable to first obtain a neuroimage (usually a CT scan) to rule out a focal intracranial mass or obstructive hydrocephalus.

If the patient has a bleeding disorder, takes anti-coagulants, or has a blood platelet count below 50,000/mm<sup>3</sup>, there is a risk of developing an epidural or subdural hematoma at the site of the LP that occasionally compresses the lumbar and sacral nerve roots. These conditions should be corrected as much as possible prior to the LP.

#### ANATOMY AND PHYSIOLOGY OF THE CSF SPACE

CSF is primarily a clear ultrafiltrate of plasma produced by choroid plexus cells. Proteins of low molecular weight (MW) reach CSF better than those of high molecular weight. As such, CSF has more albumin (MW 69 kd) than immunoglobu-

lins (MW 150 kd). In addition, some proteins are made by the choroid plexus (transferrin) and secreted into CSF. Finally, complex transport systems exist in blood vessels of the brain and the CSF pathways to remove ions or proteins (such as potassium) or deliver molecules (glucose) to the CSF. These transporter systems may be active (requiring energy such as potassium–sodium transporter from mitochondria) or passive (no

energy requirement, such as the glucose transporter) and generally maintain their respective molecules within narrow concentrations. For the above reasons, the CSF-to-plasma concentration ratios vary greatly between molecules.

Approximately 2/3 of CSF is produced by the choroid plexuses located in the lateral and fourth ventricles (Figure 3-5). The source of the remaining CSF is unclear. Choroid plexus CSF travels

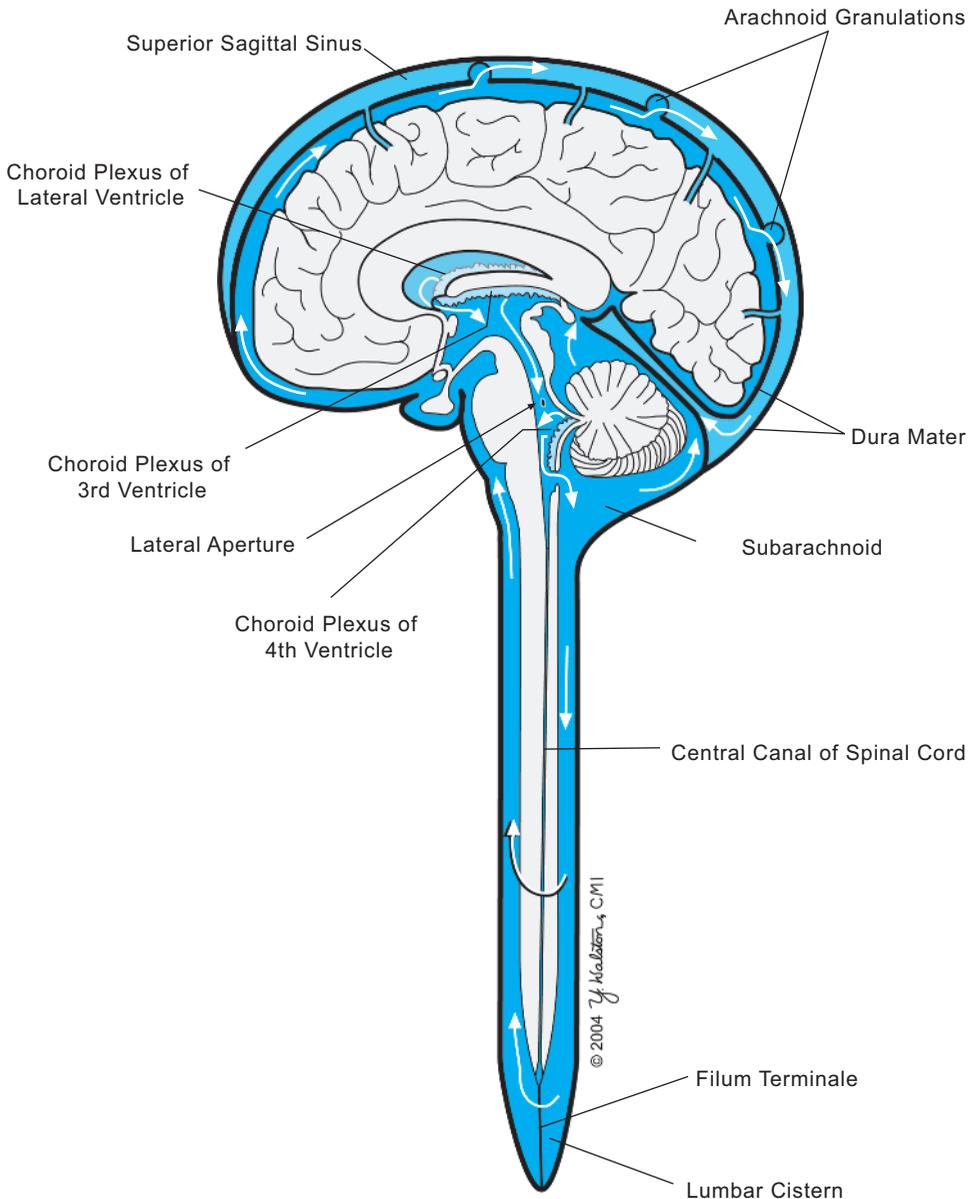


Figure 3-5 Cerebrospinal fluid flow in the central nervous system.

from the lateral ventricle into the third ventricle, and along the aqueduct of Sylvius to reach the fourth ventricle. From the fourth ventricle, CSF passes via the foramina of Luschka and Magendie to exit the cerebellum into the subarachnoid space. Blockage of CSF pathways up to this point produces obstructive hydrocephalus. In the subarachnoid space, CSF travels up through the tentorium opening and over the cerebral convexities to reach the superior sagittal sinus. Blockage of CSF pathways in the subarachnoid spaces is usually called *communicating hydrocephalus* since air introduced into the lumbar subarachnoid space can reach the lateral ventricle. At the superior sagittal sinus, CSF passes through arachnoid villi or pacchionian bodies to reach the sinus. Thus, CSF forms from blood and returns to blood.

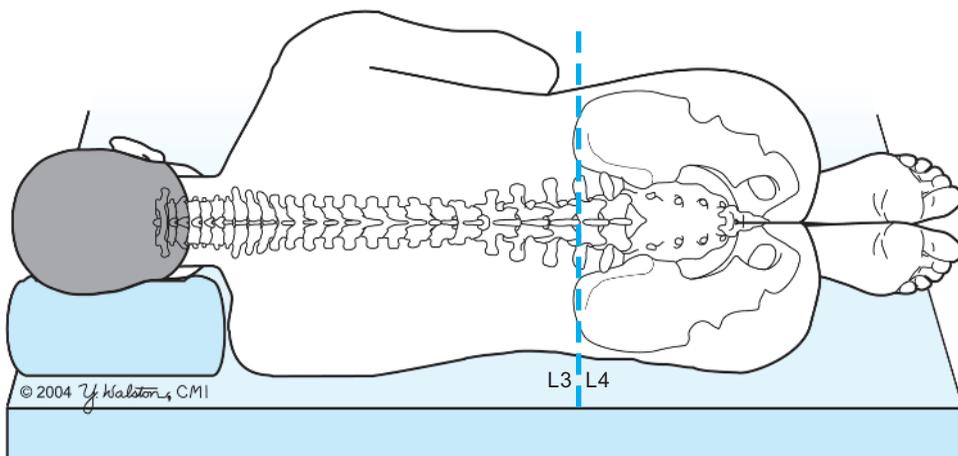
In adults, the total CSF volume is approximately 140 mL. The ventricles contain 25 mL, the spinal cord subarachnoid space 30 mL, and the remaining 85 mL are in the subarachnoid spaces around the brain. CSF is produced at a rate of 20 to 25 mL/h or 500 to 600 mL/d. Thus, CSF turns over about 4 times a day. CSF production is independent of CSF pressure (until a pressure of 450 mm CSF), but CSF absorption is dependent on CSF pressure in a linear fashion.

In adults the spinal cord descends to about T12–L1, but in small children the spinal cord may descend as low as L2. Below that level, nerve roots travel to exit appropriate neural foramina. It is at the level of the nerve roots that it is safe to perform a lumbar puncture.

#### TECHNIQUE OF LP

Written permission following informed consent is highly recommended and often required. An explanation of what will transpire will often reassure a patient and make the procedure more comfortable. Occasionally, a mild sedative is helpful in the anxious patient. Whenever possible the LP should be performed in the lateral recumbent position as this allows an accurate measure of the opening pressure. The patient, lying on a firm surface that does not sag, should be placed on the side with the knees curled toward the chin. The spinous processes should be in a horizontal line with the two iliac crests forming a perpendicular line. The intersection is usually the L3–L4 intervertebral space (Figure 3-6).

The LP needle is usually inserted in the L3–L4 space or the L4–L5 space. The skin over these areas should be thoroughly cleaned with an antiseptic solution such as betadine or alcohol. Wear sterile gloves during the procedure. Lidocaine may be injected intradermally and subcutaneously at the anticipated LP needle entry site. Normally a 20-gauge needle is used as this needle does not bend during insertion and allows accurate measurement of CSF pressure. Occasionally, smaller needles are used, but they may not allow accurate CSF pressure measurement. The LP needle is inserted bevel up through the skin and then angled slightly cephalad toward the umbilicus. It is important to keep the needle horizontal with the patient during insertion. There is usually a “pop” sensation as the



**Figure 3-6** Patient placement for lumbar puncture.

needle passes through the dura into the subarachnoid space. One can stop the procedure at any step and remove the stylet to see if CSF returns. If blood is encountered, the needle should be withdrawn and the patient repositioned before the next try, often at the next higher interspace.

Once CSF is encountered, attachment of a three-way stopcock and a manometer (which usually comes with a commercial CSF kit) allows measurement of the CSF pressure. If the pressure is elevated, relaxation of the patient and slight uncoiling the legs often reduce the pressure back to normal levels. CSF is then collected sequentially, using 4 to 5 tubes. In adults, 10 to 35 mL are usually collected, depending on the tests to be ordered. In small children, 3 to 5 mL are sufficient for standard tests in hospitals that have microchemistry facilities. Figure 3-7 lists the commonly ordered CSF tests and the tube number the tests is often ordered from. Tube 1 is the most likely to have a skin bacterial contaminant and exogenous red blood cells (RBCs) from the LP needle puncture, which may produce misleading reports if this tube is used for bacterial cultures or cell counts. It is

advisable to collect an extra tube containing several ml of CSF and mark "save" on the tube in the event that additional tests are needed. In many laboratories, the "save" CSF tube is kept frozen for at least 1 month.

The CSF should promptly be taken to the clinical laboratory, since white blood cells begin to degenerate and lyse after 1/2 hour and glucose levels may fall due to metabolism by white blood cells (WBCs). A procedure note should immediately be recorded in the patient's chart that includes indications for the LP, the location of the puncture, whether or not the spinal tap was traumatic, opening pressure, amount of fluid obtained, appearance of the fluid, and a list of tests ordered on the CSF.

NORMAL CSF VALUES

Table 3-2 lists common normal findings in adult CSF. Neonates transiently have more cells in their CSF and higher protein levels. In general for adults, the upper limit of the CSF protein level equals the patient's age. Determination of normal CSF glucose level is difficult when blood glucose is markedly elevated because high blood glucose sat-

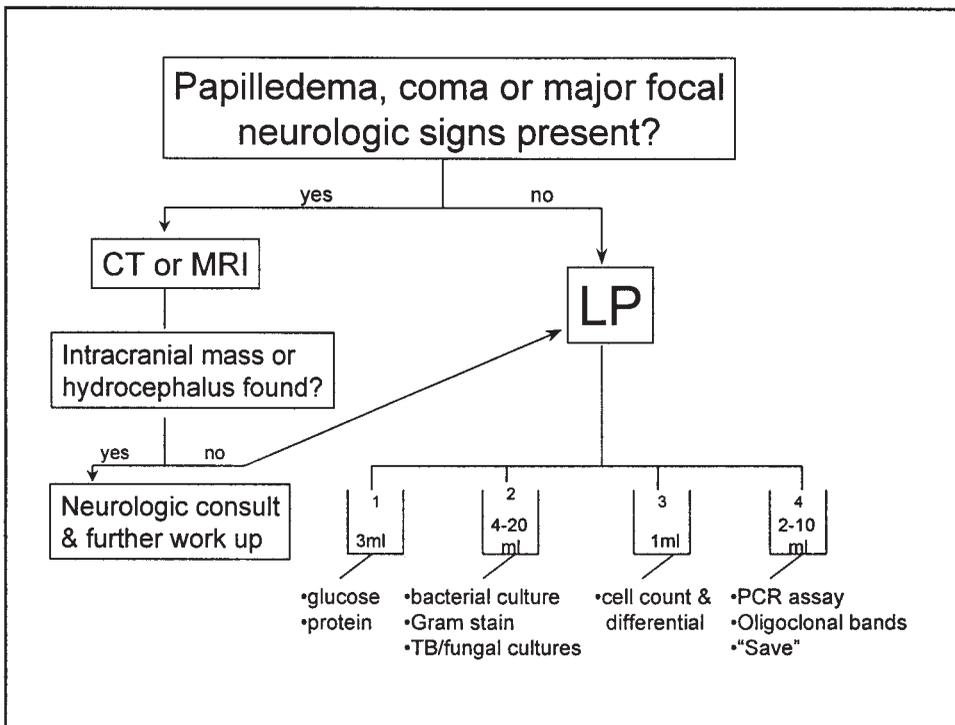


Figure 3-7 Outline of lumbar puncture algorithm.

**Table 3-2 Normal Lumbar Cerebrospinal Fluid (CSF) Findings in Adults**

Test	Normal finding
Appearance	Clear and colorless against a white background
Opening Pressure	70–180 mm CSF in recumbent position
Red Blood Cells (RBCs)	< 5 RBC/mm <sup>3</sup>
White Blood Cells (WBCs)	5–10 WBC/mm <sup>3</sup>
Differential	Mainly mononuclear cells
Total Protein	<45–<60 mg/dL depending on assay technique (<30 mg/dL if cisternal CSF, <25 mg/dL if ventricular CSF)
Percent Immunoglobulins	<15% of total protein
Oligoclonal Bands	None or rarely one band
Glucose	>40 mg/dL (usually >60% of blood glucose)
Gram Stain	Negative
Cultures	Sterile for bacteria, mycobacteria, fungi, and viruses
CSF-VDRL test	Non reactive
Cytology	No malignant cells

\* VDRL = Venereal Disease Research Laboratory.

urates the blood–CSF glucose transporter. CSF polymerase chain reaction assays are increasingly being used to diagnose infections of the CNS even when the infectious agent cannot be isolated from CSF (see Chapter 13, “Central Nervous System Infections”).

#### COMPLICATIONS OF LUMBAR PUNCTURE

A traumatic lumbar puncture occurs in 10% to 20% of LPs. It most commonly occurs when the LP needle hits a tiny vein in Batson’s plexus,

located on the dorsal side of the spinal subarachnoid space. When this happens, fresh RBCs and serum proteins from the blood and CSF enter the needle. Often the number of RBCs rapidly decreases from tube 1 to tubes 3 or 4. However, this fresh blood may falsely elevate CSF WBC and protein levels. If the RBC and WBC counts and protein measurements are done on the same tube, one simple rule of thumb is to subtract 1–2 WBC/mm<sup>3</sup> and 1 mg/dL of protein for every 1,000 RBCs/mm<sup>3</sup>. Table 3-3 (analysis of bloody CSF)

**Table 3-3 Analysis of Bloody Cerebrospinal Fluid**

CSF finding	Traumatic Lumbar Puncture (LP)	Subarachnoid Hemorrhage
Color	Tube 1 pink to red Tube 3 clearer	All tubes uniform color
Red Blood Cell Count	Higher in tube 1 than in tube 3	All tubes uniform
Color of Supernatant Fluid	Nearly colorless	Xanthochromic (yellow color)
Bilirubin	Absent	Present after first day
Clot	May occur on standing	Absent
Repeat LP at Higher Interspace	Often clear or nearly clear	Same as initial LP
Head Computed Tomography	No blood in subarachnoid space	Blood may be seen in subarachnoid spaces

gives a useful approach to distinguishing a traumatic LP from a subarachnoid hemorrhage.

While not life threatening, post-LP headaches may be quite uncomfortable. The headache begins several hours after the LP and may last for several days. The headache is usually frontal and develops when the patient moves from a lying to a sitting or standing position. Returning to a lying position relieves the headache. The incidence of post-LP headache is highest in young adult women and is uncommon in children and the elderly. In young adults the incidence is about 10%. The risk of a post-LP headache increases when larger-size LP needles are used. There is little evidence that drinking large quantities of water or lying prone prevents a post-LP headache, but lying prone for a few hours may be of benefit. With simple bed rest, the headache usually disappears.

A brain herniation from lumbar puncture is the most-feared complication, but fortunately is quite rare (less than 2% even if the CSF pressure is elevated). If the patient has markedly elevated pressure, it is still important to collect at least 5 mL of CSF for diagnostic tests before withdrawing the LP needle. Once the needle is withdrawn, CSF begins to leak out the hole in the dura. If the CSF pressure is unexpectedly markedly elevated, there are several things that should be done immediately after the LP. The patient should be observed closely for signs of neurologic deterioration over the next 8 hours. Prompt neuroimaging (CT or MRI) often identifies the cause of elevated CSF pressure. A secure intravenous line may be established should mannitol administration be required. Notification of a neurosurgeon that a potential problem exists is helpful should a surgical cause of the increased CSF pressure be identified. If brain herniation begins, the patient should be given intravenous (IV) mannitol, intubated, and hyperventilated to lower intracranial pressure.

## Neuroimaging Tests

CT and MRI are the most widely used imaging techniques because they yield high resolution of the brain and surrounding structures, they are safe, they are performed in a reasonable period of time, and they are widely available in the United States. Both CT and MRI images are to be presented as if one is looking at the patient upward

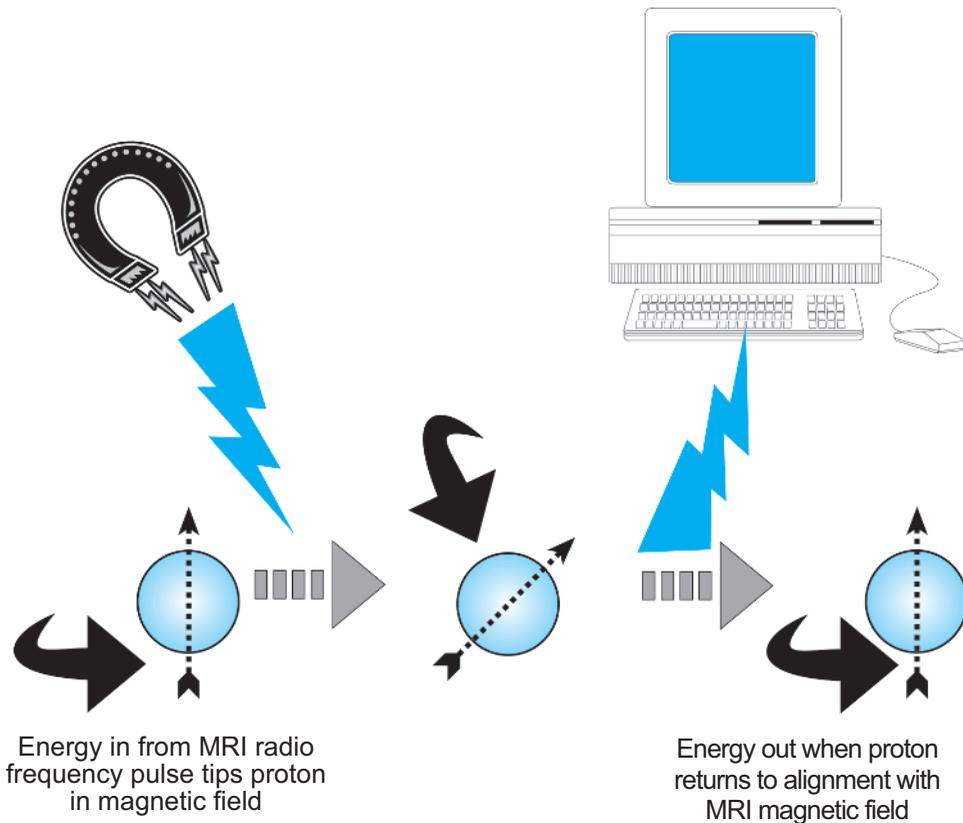
from the foot of the bed. Thus, *the right side of the brain is located on the left side of the brain image.*

CT uses a beam of x-rays shot straight through the brain. As the beam exits the other side, it is blunted or attenuated slightly because it has hit dense living tissues on the way through the head. Very dense tissue, like bone, blocks many x-rays; the brain blocks some; and CSF and water block even less. As with conventional x-ray, bone appears bright because its high density blocks x-rays from darkening the film. Conversely, less-dense objects, such as CSF or fat, appear dark since x-rays can penetrate to expose the film. X-ray detectors positioned around the circumference of the scanner collect attenuation readings from multiple angles, and a computerized algorithm constructs the image of each slice. A standard CT creates horizontal (axial) brain slices that are about 1 cm thick and in a different plane than that used by MRI. The total x-ray exposure from CT is about that of a chest x-ray. Presently only a few seconds are required to obtain one brain slice and 15 to 20 minutes for the entire brain.

MRI uses different physical principles than CT to create brain images. When brain protons are placed in a magnetic field, they oscillate. The frequency of oscillation depends on the strength of the magnetic field. Protons are capable of absorbing energy if exposed to electromagnetic energy at the frequency of oscillation. After the proton absorbs energy, the nucleus releases or reradiates this energy and returns to its initial state of equilibrium. The reradiation or transmission of energy by the nucleus is what is observed as the MRI signal (Figure 3-8).

The return of the nucleus to equilibrium occurs over time and is governed by 2 physical processes: (1) T1, the time for relaxation back to equilibrium of the component of the nuclear magnetization that is parallel to the magnetic field and (2) T2, the time for relaxation back to equilibrium of the component of the nuclear magnetization that is perpendicular to the magnetic field. Contrast between brain tissues depends upon the proton density, T1, and T2. MRI signals can be “T1- or T2-weighted” to accentuate select properties by changing the way the nuclei are initially subjected to electromagnetic energy.

T1-weighted images yield the sharpest and most accurate brain anatomy but less information about brain pathology. T2-weighted images better



**Figure 3-8** Basic principles of magnetic resonance imaging (MRI).

demonstrate brain pathology but are less suitable for brain anatomy. Table 3-4 gives tissue types that are bright and dark on T1- and T2-weighted images. When brain pathology is located adjacent to ventricles with CSF, it may be difficult to distinguish CSF from the lesions on T2-weighted images. In these cases, intermediate-weighted images (proton density images) or fluid-attenuated inversion recovery (FLAIR) images are helpful. Diffusion-weighted MRI scans help identify acute infarctions.

The key to identifying the type of MRI image lies in the CSF. *On T1-weighted image CSF is dark and on T2-weighted images, CSF is bright.*

Patient safety is of some concern when the patient is around the MRI machine due to the magnet's high magnetic field. Most MRI machines are 1.5 Tesla, meaning the magnet has a field strength 30,000 times that of earth. Ferromagnetic objects on the patient's or attendant's clothing can become missiles and fly inside the magnet. Cardiac

pacemakers are contraindicated. Most modern surgical clips and orthopedic appliances are MRI safe, but older neurosurgical clips may be dangerous. Should a medical emergency occur while the patient is within the magnet, the patient must be removed from the MRI scanner room before attempting resuscitation since ventilators, crash carts, and emergency personnel often carry ferromagnetic objects.

As seen in Table 3-5, MRI is the superior neuroimaging test for most neurologic illnesses. Table 3-6 compares the advantages of MRI and CT. In several new applications of magnetic resonance, magnetic resonance spectroscopy (MRS) can evaluate levels of brain metabolites such as *N*-acetylaspartate, choline, creatine, myoinositol, and lactate. Often the magnet employed is of higher strength (2.0–4.0 Tesla). MRS presently has few clinical indications but researchers are examining methods of biochemically identifying brain abnormalities such as brain tumors, abscesses, etc.

**Table 3-4 Signal Intensities and Densities of Tissue Types in Neuroimaging**

Neuroimaging	Bright	Dark
MRI T1 weighted	Fat Methemoglobin Gadolinium contrast	Bone or dense calcium CSF Edema or water Air Flowing blood
MRI T2 weighted	Edema or water CSF Methemoglobin (extracellular)	Bone or dense calcium Air Fat Flowing blood Iron-laden tissues Hemosiderin Deoxyhemoglobin Methemoglobin (within RBC)
CT	Bone Blood not in vessels CT contrast material Thrombosis of major vessels	CSF Edema or water Fat Air

CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging; RBC = red blood cell.

Functional magnetic resonance imaging (fMRI) evaluates changes in cerebral blood flow in response to local changes in neuronal firing patterns. Thus, fMRI gives information about structure and indirect information about function. Neuroimaging tests are safe, expensive, comfortable, and take up to 1 hour.

### Single-Photon/Positron Emission Computed Tomography (SPECT or PET)

When radiolabeled compounds are intravenously injected in tracer amounts, their photon emissions can be detected, much like x-rays in CT. The images are often shown in a color scale that represents the amount of the labeled compound accumulated in specific brain regions. Various compounds may reflect blood flow, oxygen or glucose metabolism, or concentrations of specific neurotransmitter receptors. These tests are safe, expensive, mildly uncomfortable, and take 1 hour.

### Brain, Nerve, and Muscle Biopsy

A small piece of brain, meninges, peripheral sensory nerve, or muscle is surgically removed for histologic examination and culture for infectious agents. Indications for a biopsy include (1) determining the etiology of a brain mass, (2) culturing a suspected brain infection that has not been isolated from CSF or other body sites, and (3) establishing a specific diagnosis of a myopathy or neuropathy. Since the biopsy destroys tissue, it is performed usually when other safer diagnostic tests fail or during surgery to debulk a brain tumor of unknown type. A biopsy is expensive, uncomfortable to the patient, and has a risk of complications. For example, a brain biopsy has a 5% risk of subsequent seizures, and all biopsy sites can become infected.

### Molecular/Genetic Neurologic Tests

The completion of the Human Genome Project and improving methods to link disease pheno-

**Table 3-5 Commonly Ordered Neuroimaging for Neurologic Conditions**

Imaging Indications	Test Commonly Ordered
Head Trauma	
Acute	CT
Old	MRI
Cerebral Hemorrhage	CT
CNS Infection	MRI with gadolinium
Acute Stroke	MRI with diffusion-weighted images
Seizures	MRI
Brain Tumor	MRI with gadolinium
Multiple Sclerosis	MRI
Dementia	MRI
Back Pain with Radiculopathy	MRI
Spinal Cord Disease and Myelopathy	MRI
Atypical Headaches	MRI

CNS = central nervous system; CT = computed tomography; MRI = magnetic resonance imaging.

types to specific gene loci enable the diagnosis of many neurologic genetic diseases. Most disease-causing mutations consist of single base substitutions leading to amino acid substitutions (missense mutations; neurofibromatosis type 1), premature translation stop signals (nonsense mutations; Duchenne and Becker muscular dystrophies), or abnormal ribonucleic acid (RNA) transcript splicing. Other clinically important mutations come from deoxyribonucleic acid (DNA) deletions, DNA duplications (Down syndrome), or abnormal expansion of unstable trinucleotide repeats (Huntington's chorea and spinocerebellar atrophy). Recessive genetic diseases usually derive from mutations, causing production of abnormal enzymes from both chromosomes so the normal enzyme from the opposite chromosome cannot compensate. Total or severe loss of important enzyme functions

**Table 3-6 Comparison of Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) Techniques**

Advantages of MRI
• Better imaging of brain located adjacent to bone
• Superior brain anatomy
• Detection of smaller brain lesions
• Better detection of subtle central nervous system pathology such as low-grade tumors
• Can visualize major neck and cerebral arteries and veins (magnetic resonance angiography)
• No ionizing radiation so safer than CT, especially during pregnancy
Advantages of CT
• Faster imaging time so restless, uncooperative patients can be scanned with fewer movement artifacts
• Ferromagnetic objects may be in or on the patient
• Less claustrophobia
• Better detection of subarachnoid hemorrhage, brain calcifications, and bone fractures

results in metabolic diseases affecting brain development or preventing normal turnover of brain proteins, allowing them to abnormally accumulate in neurons. Dominantly inherited genetic diseases are mainly caused by mutations affecting important proteins.

The genetic mutations of many genetic neurologic diseases can be detected using non-CNS host tissues, such as WBCs, skin biopsy, or mouth mucosa cell scrapings. Assays for specific enzymes can be performed, such as hexosaminidase A to diagnose Tay-Sachs disease. Chromosomal banding and spectral karyotyping can detect gross deletions or duplications of chromosomal DNA. Cellular DNA can be screened for specific genetic mutations by several methods, including polymerase chain reaction (PCR) assays, automated fluorescent sequencing, Southern blotting, and fluorescence *in situ* hybridization (FISH).

While these tests are constantly improving and new genetic mutations are being identified, molecular genetic tests have limitations: (1) failure to

detect a given mutation does not rule out the suspected disease, as the mutation site may be different from those searched for in the assay; (2) different mutations in the same gene can produce different phenotypes; and (3) mutations in the same gene can produce different phenotypes. In addition, incomplete penetrance, age-dependent onset, and other genes often modify the disease's phenotypic expression and rate of progression.

A major advance in the diagnosis of infectious agents affecting the CNS is the PCR assay. These assays now exist for many viruses, bacteria, mycobacterium, fungi, and protozoa. Since the PCR assay identifies only a small, but unique, fragment of the infectious agent DNA or RNA, the nucleic acid does not have to be fully intact or part of an infectious organism. As such, the PCR test often is positive when culture of the infectious agent is negative. The test is performed on CSF or biopsy tissue. Compared with conventional isolation methods, the PCR assay is sensitive, rapid (can be completed in hours to 1 day), less expensive, and safer (does not require infectious organisms).

PCR works on the following basic principles. First, unique short DNA fragments, called *primers*, are chemically synthesized as oligonucleotide primers. Second, the primers, free DNA nucleo-

tides, and heat-stable DNA polymerase are added to the DNA mixture, which contains DNA from the microorganism in question. The mixture is heated to melt and separate the double-stranded DNA and then cooled, allowing the primers to hybridize to their complementary sequences on the separated strands of the microorganism's DNA. The DNA polymerase enzyme adds nucleotide bases to the ends of the primers to create a long segment of double-stranded DNA. Third, another application of heat splits the new DNA fragments apart to allow the cycle to repeat doubling the number of DNA templates. Using automated equipment, it is possible to make millions of copies of the desired template within hours. Fourth, since the DNA template molecules are all the same length and composition, they can be detected by gel electrophoresis or other methods.

## RECOMMENDED READING

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## 4 DISORDERS OF MUSCLE

### Overview

The human body has over 600 muscles; their bulk comprises about 40% of the total body weight. Muscles are divided into skeletal muscles (responsible for voluntary movement and innervated by motor neurons of the anterior horn or brainstem), smooth muscle (involuntary muscles of the gastrointestinal tract, genitourinary tract, blood vessels, and skin innervated by autonomic nerves), and cardiac muscle (heart muscle innervated by autonomic nerves). Each muscle type has distinct morphologic and biochemical characteristics that separate them and enable diseases to involve one or more muscle types. In simple terms, a muscle fiber is a long multinucleated cell that contains myofibrils for contraction and abundant mitochondria for energy production. Diseases of skeletal muscle are called by several general names: myopathy, implying all types of muscle disease; myositis, implying inflammation in the muscle; and muscular dystrophy, implying degeneration of muscle, often hereditary.

The first step in diagnosing a muscle disease is to distinguish it from other causes of weakness (Table 4-1). However, there are exceptions to Table 4-1. For example, some skeletal muscle disorders are episodic (hyper- or hypokalemic periodic paraly-

sis), some involve distal to a greater extent than proximal muscles (distal and myotonic muscular dystrophies), some produce myotonia or sustained muscle contractions (myotonic muscular dystrophy), and some involve specific muscle groups (lid muscles and swallowing muscles in oculopharyn-

**Table 4-1 Common Features of Primary Skeletal Muscle Diseases**

• Proximal weakness greater than distal weakness
• Symmetrical weakness
• Muscle atrophy proportional to degree of weakness
• Doughy feel to muscle on palpation
• Hypotonic muscle
• Slow progression of weakness
• Weakness rarely painful
• Loss of deep tendon reflexes proportional to degree of weakness
• No sensory loss
• Serum creatine kinase often elevated early in disease
• Electromyography shows myopathic features

geal muscular dystrophy). Thus for unknown reasons all skeletal muscles are not equally susceptible to a given type of muscular dystrophy in spite of their apparent similarity in structure.

Table 4-2 lists differences between the various types of weakness that are helpful for localizing weakness due to a muscle disorder.

Muscle diseases are divided into 4 broad categories: muscular dystrophy due to genetic abnormalities; channelopathies with abnormal sodium, calcium, or potassium membrane ion channels; inflammatory myopathies; and secondary endocrine myopathies.

## Duchenne Muscular Dystrophy (Muscular dystrophies)

### Introduction

Muscular dystrophies are genetically determined disorders that have a wide variation in age of

onset, sex distribution, location of maximal muscle atrophy, and phenotypic signs. The most common and most serious muscular dystrophy is Duchenne muscular dystrophy (DMD), a lethal childhood disorder associated with a marked deficiency or absence of dystrophin. A large gene on the X chromosome at Xp21 encodes dystrophin. DMD is the most common disease associated with genetic mutations of the dystrophin gene. Collectively these diseases are called dystrophinopathies. As DMD is transmitted by X-linked recessive inheritance, nearly all patients are male. About 10% of female carriers have mild muscle weakness.

The incidence of DMD is 30/100,000 male births, with prevalence in the general population of 3/100,000. New mutations account for about 1/3 of cases.

### Pathophysiology

The dystrophin gene is among the largest known, spanning about 2.3 megabases of DNA or almost

**Table 4-2 Distinguishing Characteristics of Limb Weakness**

Characteristic	Upper Motor Neuron (Corticospinal Tract)	Lower Motor Neuron (Peripheral Nerve)	Distal Polyneuropathy	Neuro-muscular Junction	Skeletal Muscle
Muscle Involved	Distal more than proximal and often unilateral	Distal more than proximal	Distal more than proximal	Proximal more than distal	Proximal more than distal
Muscle Atrophy	Minimal	Marked	Moderate	Minimal	Moderate
Normal Strength that Quickly Fatigues	No	No	No	Yes	No
Fasciculations	No	Common	No	No	No
Deep Tendon Reflexes	Increased	Decreased to absent	Decreased to absent	Normal or slightly decreased	Normal to decreased proportional to weakness
Sensory Loss	May be unilateral	Yes	Yes	No	No
Positive Family History	Uncommon	Uncommon	Uncommon	Uncommon	Common
CK Elevation	No	No	No	No	Yes
EMG and nerve conduction findings	None	Denervation on EMG or slow motor nerve conduction velocity	Abnormal EMG and nerve studies	Minimal changes on EMG or nerve studies	Myopathic motor units on EMG

CK = creatine kinase; EMG = electromyogram.

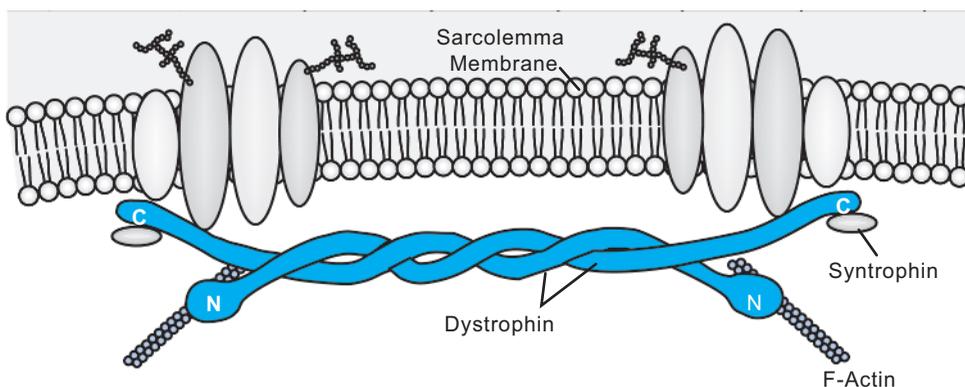
1% of the entire X chromosome. Muscle dystrophin is a large 427-kd molecular weight protein of 3,685 amino acids that is found primarily within skeletal, smooth, and cardiac muscle. Dystrophin isoforms are also present in cortical neurons, Purkinje cell neurons, glia, and Schwann cells. Dystrophin accounts for 5% of sarcolemmal cytoskeletal proteins in muscle. The protein is rod shaped and resides just beneath the sarcolemmal membrane as two parallel fibers (Figure 4-1). The amino terminus is attached to actin and the carboxyterminus binds to a transmembrane protein complex that is located on the transmembrane. In muscle, dystrophin links myofibrillar elements with the sarcolemma, affording stability and flexibility to the muscle fiber of patients with DMD.

Of these patients, 75% demonstrate large-scale deletions in the gene or have partial gene duplications; the remainder are poorly characterized. Nearly 80% of deletions occur in the center of the protein. The remaining 25% of patients have small or point mutations. Frame-shift mutations usually produce truncated molecules lacking the carboxyterminus and thus produce DMD. Non-frame-shift mutations usually result in an abnormal protein that has a carboxyterminus and can partially function. Mutations of this type are often seen in Becker muscular dystrophy, a milder form of DMD where the amount of dystrophin is less than normal but not absent. Thus, the old adage of “1 gene = 1 protein = 1 disease” is an oversimplification.

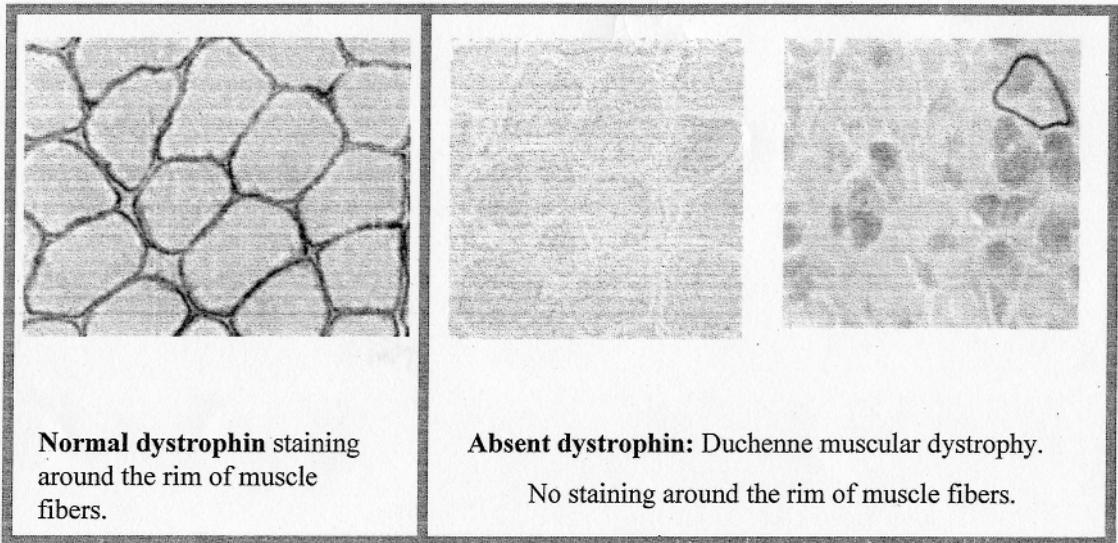
Dystrophin gene mutations that cause DMD result in either the absence of dystrophin protein production or markedly truncated proteins that cannot attach to the transmembrane protein complex and are rapidly catabolized. The net result is the virtual absence of dystrophin and the dystrophin-associated protein (DAP) complexes along the sarcolemmal membrane. Quantitative studies of dystrophin have shown less than 3% of normal dystrophin content is present in DMD muscle (Figure 4-2).

The absence of dystrophin leads to membrane instability, myofiber leakiness of creatine kinase (CK), and susceptibility to injury from normal muscle contractions. Over time, the damaged muscle cell wall allows abnormal influxes of calcium and subsequent activation of cell proteases with amplification of disturbed calcium homeostasis. This results in fiber necrosis, secondary inflammation, and apoptosis.

Although mature muscle fibers are postmitotic, skeletal muscle contains mononuclear muscle precursor cells that proliferate and fuse in response to stimuli from degenerating muscle fibers. Since these regenerating muscle fibers also lack dystrophin, the process repeats itself. Over time, fibrosis and scarring develop in the muscle, and fat cells invade, replacing the degenerating muscle cells. The net process may transiently give rise to enlarged doughy muscles that have a pseudohypertrophic appearance.



**Figure 4-1** Dystrophin molecule beneath external muscle membrane (sarcolemma).



**Figure 4-2** Quantitative studies of dystrophin have shown less than 3% of normal dystrophin content is present in Duchenne muscular dystrophy muscle (Courtesy of Alan Pestrank, MD).

### Major Clinical Features

Although children with DMD have disease activity in the neonatal period (elevated serum CK and necrosis on muscle biopsy) they rarely have clinical symptoms until age 3 to 4 years. Parents usually report difficulty in running or climbing, frequent falls, and enlargement of the calf muscles, which feel firm and rubbery. By 4 to 5 years of age, the gait becomes wide-based and waddling and the child often walks on his or her toes because of heel cords contractures. The weakness is greatest in proximal muscles, producing a Gowers maneuver (placing hands on the knees and climbing up the thighs to stand) (Figure 4-3).

In the early school years, the limb weakness progresses and is accompanied by excessive lordosis. There is relative clinical sparing of extraocular muscles and muscles of bladder and bowel sphincters, as for unknown reasons these muscles lack dystrophin. By age 10 to 12 years, the child is unable to walk and is confined to a wheelchair. Deep tendon reflexes are lost and joint contractures appear at the hip flexors and heel cords. By late teens the weakness is profound, scoliosis is marked, and joint contractures are frequent.

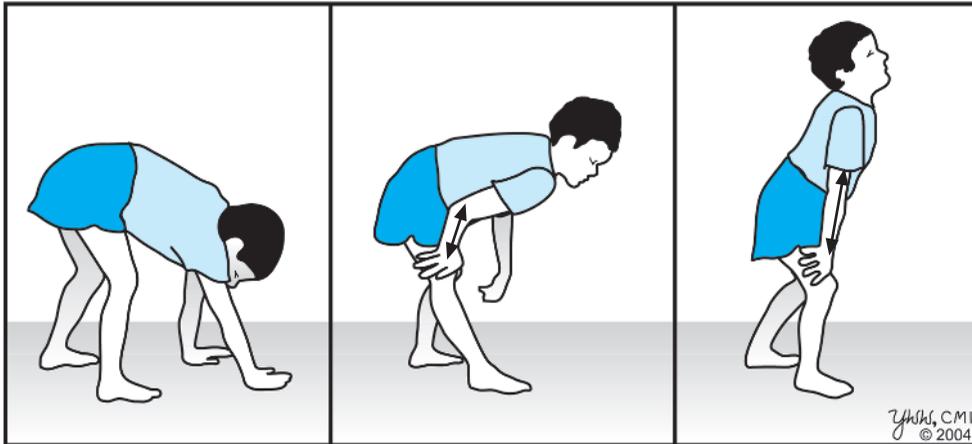
About 25% of children have IQ scores below 75 and the average IQ score is 1 standard deviation below the mean. Some children develop smooth muscle involvement with gastric hypomotility and constipation. Cardiomyopathy, cardiac muscle damage, slowly develops. Kyphoscoliosis and weakness of respiratory muscles produce a decreasing lung vital capacity and low maximal inspiratory and expiratory pressures.

The terminal stages of DMD are characterized by recurrent pulmonary infections and often congestive heart failure. The age of death ranges from 10 to 30 years, with a mean of 18 years. Only 5% live beyond 26 years.

Female carriers are usually normal, but 10% demonstrate mild weakness of proximal muscles. Carriers usually can be identified by pedigree analysis and presence of mildly elevated serum CK levels. (CK elevation is not seen in all carriers.)

### Major Laboratory Findings

In young children, serum CK level is always markedly elevated, often 100 times above the normal upper limit. In the late stages of DMD, the CK



**Figure 4-3** Gowders maneuver.

level falls as muscle mass disappears. The electrocardiogram is abnormal in 2/3 of patients.

The EMG demonstrates myopathic motor unit potentials and occasionally fibrillation potentials from segmental necrosis of muscle fibers (see Chapter 3, “Common Neurologic Tests”).

Muscle biopsy demonstrates a mixture of fiber sizes, containing necrotic, regenerating, and large hyaline (hypercontracted, opaque, or large dark) fibers. Necrotic fibers have a glassy appearance from loss of the intermyofibrillar membranous network and are invaded by macrophages (Figure 4-2). Fiber type grouping of remaining muscle fibers is normal. Electron microscopy of non-necrotic muscle fibers demonstrates defects in the plasma membrane, where abnormal calcium influx occurs. Later in the disease, fibrosis and fatty replacement of muscle fibers is seen. Immunohistochemical staining demonstrates absence or near absence of dystrophin along the sarcolemma membranes.

It is now possible to use PCR analysis to detect deletions in the dystrophin gene to account for about 75% of all DMD cases. However, the PCR study does not determine whether there is a frame-shift abnormality. This makes it more difficult to separate DMD from Becker’s dystrophy, which contains the carboxyterminus. If the DMD mutation is a deletion, prenatal diagnosis can be made by PCR studies of chori-

onic villus tissue. If the type of DMD mutation is unknown, experimental studies of 19-week fetal muscle biopsies can determine the presence or absence of dystrophin.

### Principles of Management and Prognosis

Management must be multidisciplinary. No drugs have yet proven to reverse the pathologic process. However, corticosteroid administration may improve strength and performance for up to 1 year. Management involves use of joint bracing and prevention or release of contractures to maintain walking for as long as practical. The wheelchair should be viewed as a passport to mobility and not a failure to walk. Once the child is confined to a wheelchair, attention should be directed toward posture and bracing to minimize scoliosis. Occasionally, surgical procedures to improve posture or correcting joint contractures are indicated. Education should proceed in a normal fashion. Terminally, attention is directed to maximizing pulmonary function and minimizing respiratory infections.

Considerable research is underway to replace the mutated dystrophin gene by introduction of a normal gene into muscle fibers via a plasmid or viral vector or by inoculation of genetically normal myoblasts, which fuse with the patient’s regenerat-

ing muscle fibers. To date all results have been disappointing.

## ***Dermatomyositis (Inflammatory myopathy)***

### **Introduction**

Inflammatory myopathies are a heterogeneous group of diseases characterized by muscle inflammation. In some, there is an infectious etiology (trichinosis or viral myositis) but in most the etiology is unknown. Dermatomyositis (DM) has an immune-mediated pathogenesis. While DM can occur at any age, children from ages 5 to 14 years are the most likely to become symptomatic. As in most autoimmune disorders, females are more often affected, but the majority of patients lack a family history of the disorder. The estimated incidence is 0.6/100,000, but the incidence is 1/100,000 in adults. African Americans appear to be more commonly susceptible than caucasian Americans. Patients with DM have a slightly higher incidence of malignancies found at the time or within a few years of diagnosis. An association of collagen vascular diseases such as systemic lupus erythematosus and Sjögren syndrome has been noted.

### **Pathophysiology**

The etiology of this disease is unknown, but is thought to be the consequence of differing immune-mediated processes of blood vessels.

Dermatomyositis appears to be an antibody-mediated disease in which complement is activated by deposition of membrane attack complexes in blood vessels. Destruction of the blood vessels leads to ischemia, producing muscle fiber necrosis, microinfarcts, and perifascicular atrophy (at the edges of a muscle fascicle). Capillary destruction is not limited to muscles, but may occur in skin (heliotrope rash of face, eyelids, and sun-exposed areas) and other organs such as the lungs (interstitial lung disease) and heart (cardiomyopathy).

Patients may have autoimmune antibodies that are directed against poorly characterized cellular targets such as cytoplasmic molecules, signal-recognition particles, and myositis-specific epitopes. For example, anti-Jo-1 antibodies targeted against his-

tidyl transfer (t)-RNA synthetase can be seen in serum of both polymyositis (PM) and DM. The clinical significance of these autoantibodies is unclear. However, an elevated anti-Jo-1 antibody titer may signal increased disease activity and an increased risk of developing interstitial lung disease.

### **Major Clinical Features**

Typically, weakness is proximal and first noted in a symmetrical fashion in muscles of the shoulder and pelvic girdle. Muscle pain and soreness is uncommon. As the disease progresses, the patient may develop dysphagia and neck weakness. Occasionally respiratory muscles may become involved. The early skin rash is characterized by erythema (heliotrope appearance) accompanied by edema of the subcutaneous tissue affecting mainly the periorbital, perioral, malar, and anterior chest regions. Skin exposed to sunlight may also develop a similar rash. The rash often progresses to cause scaling, pigmentation, depigmentation, and skin with a brawny induration. Linear erythematous discoloration may surround nail beds.

Interstitial lung disease occurs in about 10% of patients, usually after years of disease. Patients experience a nonproductive cough and dyspnea from bronchiolitis obliterans, interstitial pneumonia, and/or diffuse alveolar damage.

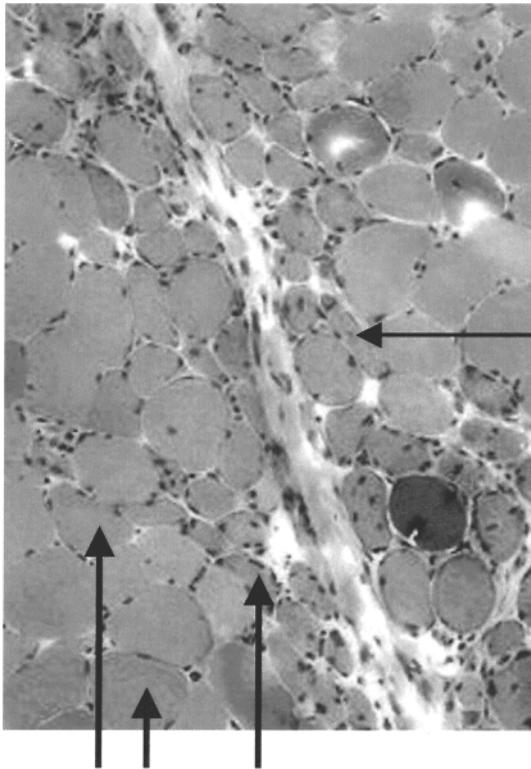
### **Major Laboratory Findings**

Serum CK levels are elevated (3–30 times above normal). A few patients have autoimmune antibodies, including anti-Jo-1 antibodies and anticytoplasmic antibodies, anti-signal-recognition particle antibodies, and antibodies against Mi-2 antigens.

The EMG demonstrates an irritative myopathy with myopathic changes (brief, small-amplitude, abundant, polyphasic motor units) and signs of denervation from the associated inflammation (fibrillations and positive sharp waves).

Muscle biopsy in DM demonstrates muscle changes in the perifascicular region. Myopathic changes include necrosis and regeneration, muscle fiber atrophy (Figure 4-4), and a reduction in cytochrome oxidase activity. Inflammatory changes are seen but do not correlate with severity of muscle disease.

Blood vessels demonstrate perivascular collections of inflammatory cells, arteritis,



Regenerating muscle fibers (basophilic cytoplasm, large nuclei with enlarged nucleoli) are seen in the perifascicular area

Muscle fiber size is variable

**Figure 4-4** Muscle biopsy of dermatomyositis. (Courtesy of Alan Pestronk, MD.)

phlebitis, intimal hyperplasia of arteries and veins, and occlusion of vessels by fibrin thrombi. Adjacent to occluded vessels are ischemic and infarcted muscle fibers. In the majority of children with DM and in some adults with DM, there are immune complexes containing IgG, IgM, and complement (C3) within the walls of arteries and veins. These muscle and skin angiopathic changes at the electron microscope level are virtually diagnostic.

### Principles of Management and Prognosis

Before treatment, a clear diagnosis is needed, which usually requires a typical clinical history, characteristic EMG findings, and a muscle biopsy showing inflammatory myopathy or diagnostic blood vessel damage. Corticosteroids represent the first line of therapy, with an initially high dose that is tapered as the patient regains muscle strength and the CK level falls. If corticosteroids fail or adverse reactions develop, patients are given

immunosuppressants such as azathioprine or methotrexate. These drugs may require 3 to 6 months of treatment before they are effective. Human immune globulin (IVIg) may be given initially to severely affected individuals.

The duration of DM disease activity in children is variable and may last several months to 4 years before becoming inactive. In adults the 5-year survival is 90% and the 10-year survival is 80%. Individuals with malignancies, interstitial lung disease, or cardiomyopathy fare worse.

### Primary Hyperkalemic Periodic Paralysis (channelopathies)

#### Introduction

Channelopathies are a group of diseases with abnormal channels resulting from genetic disorders. Channels are pores in cell membranes that allow ions to enter or exit a cell to depolarize or

hyperpolarize the cell. These macromolecular protein complexes with the lipid membrane are divided into distinct protein units called *subunits*. Each subunit has a specific function and is encoded by a different gene. A channel may be non-gated, directly gated, or second-messenger-gated. Important directly gated channels include voltage-gated channels (sodium, potassium, calcium, and chloride) and ligand-gated channels (acetylcholine, glutamate,  $\gamma$ -aminobutyric acid (GABA), and glycine).

Genetic mutations in critical areas of a channel can produce an abnormal gain of function (additional properties not present in the normal protein) or loss of function (loss of properties present in the normal protein). Channelopathy diseases primarily affect excitable cells such as muscle fibers and neurons and produce signs and symptoms that are often episodic.

Primary hyperkalemic periodic paralysis (hyperkalemic PP) belongs to a group of channelopathies with mutations in the voltage-gated sodium channel. Other sodium channelopathies include familial generalized epilepsy with febrile seizures, paramyotonia congenital, and hypokalemic periodic paralysis.

### Pathophysiology

Hyperkalemic PP is due to a dominant mutation in chromosome 17q35 that affects the  $\alpha$ -subunit (SCN4A) of the sodium channel (Figure 4-5). Of all cases, 90% are the result of two mutations, one of which produces both periodic flaccid weakness and myotonia.

The muscle membrane in a patient with hyperkalemic PP contains 2 types of sodium channels. A normal channel from the normal gene activates (opens) and then inactivates (closes) rapidly. However, the mutated sodium channel activates appropriately but inactivates abnormally slow.

In normal muscle, hyperkalemia causes a few normal sodium channels to open. The subsequent slight membrane depolarization is rapidly corrected as the channels close before the depolarization is sufficient to cause muscle contraction. However, in hyperkalemic PP muscle, the hyperkalemia opens both the normal sodium channel and the mutated sodium channel. The mutated sodium channel remains open for a prolonged period, allowing excess entry of sodium into the

muscle cell. The excess intracellular sodium in turn produces a prolonged depolarization. The net result is that the depolarized muscle fiber becomes paralyzed, electrically unexcitable, and nonresponsive to future nerve stimulation.

The sodium influx allows efflux of intracellular potassium into the extracellular space and also causes extracellular water to enter the muscle fiber, resulting in hemoconcentration. Both result in a further rise in serum potassium level. The elevated potassium level triggers more muscle fibers to become persistently depolarized and the entire muscle rapidly becomes paralyzed. The cycle ends when the serum potassium level returns to normal by the kidney's excretion of potassium and likely by other corrective measures. The duration of paralysis may be 15 minutes to hours.

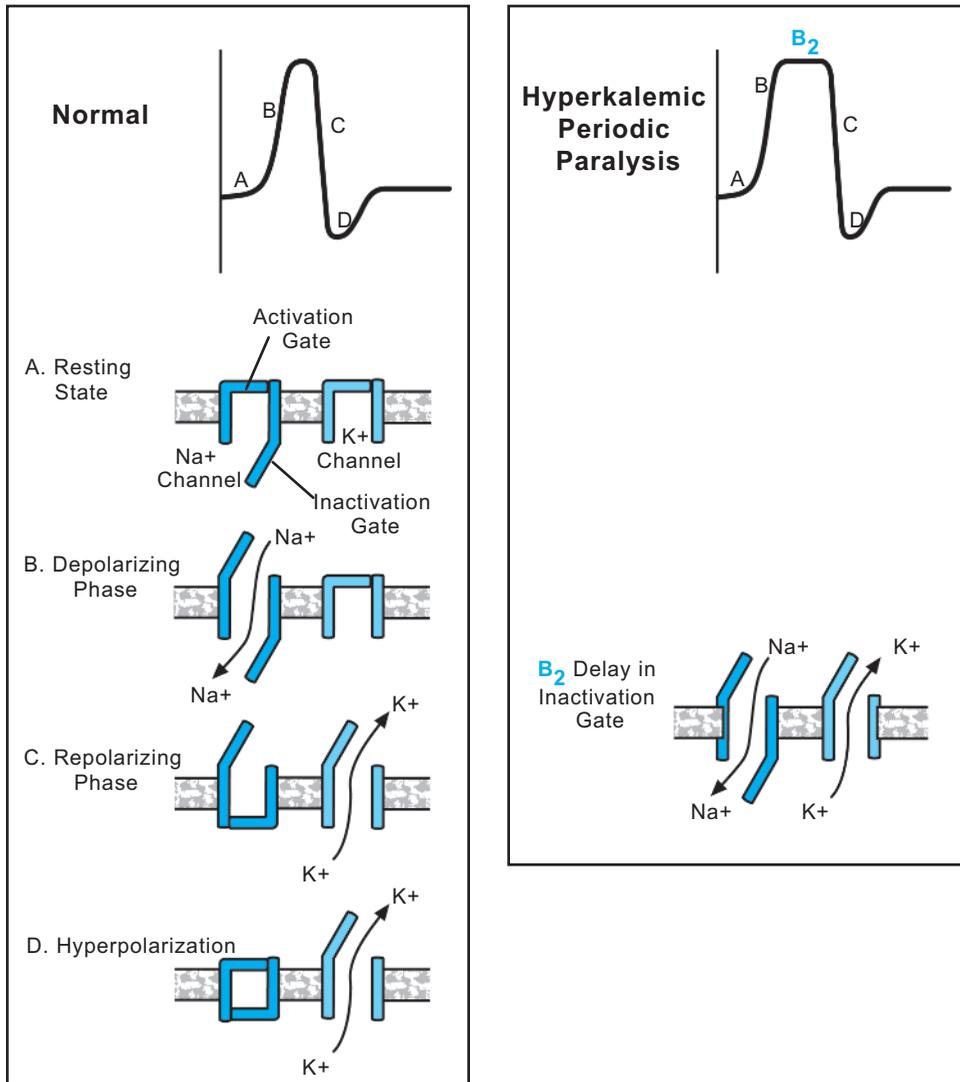
Normal individuals can develop muscle paralysis if their serum potassium level rises above 7 mmol/L. Hyperkalemia may occur in renal failure, adrenal insufficiency, and exposure to the diuretic spironolactone.

### Major Clinical Features

The paralysis attacks usually begin in the first decade of life and are infrequent. With increasing age the attacks become more frequent. In severe cases, they occur daily. Most episodes occur in the morning before breakfast. Attacks during the day are often precipitated by strenuous exercise followed by rest. Other triggers include consumption of excess potassium, emotional stress, fasting, a cold environment, and corticosteroid administration.

At the start of an attack the patient may experience paresthesias or sensations of increased muscle tension. The patient then develops a flaccid generalized weakness and cannot move the arms, legs, and trunk. The weakness spares respiration muscles, cranial nerves, and bladder and bowel sphincters. The attack lasts 15 minutes to 1 hour before spontaneously disappearing. Afterwards, strength returns to normal and the individual commences normal activity. Over years, patients with severe hyperkalemic PP may develop permanent muscle weakness.

One mutation causes varying amounts of myotonia between attacks. The clinical symptom of myotonia is essentially a slowing of relaxation of a normal muscle contraction and is commonly interpreted by the patient as "stiffness." Commonly the



**Figure 4-5** Hyperkalemic periodic paralysis is due to a dominant mutation in chromosome 17q35 that affects the  $\alpha$ -subunit (SCN4A) of the sodium channel.

patient cannot easily release a grip on an object. A cold environment often makes myotonia worse.

### Major Laboratory Findings

During an attack, the serum potassium level rises up to 5 to 6 mmol/L but rarely reaches cardiotoxic levels. The serum sodium level falls slightly as the ion enters muscle fibers. Renal excretion of potassium occurs, with elevated urine potassium levels. The serum CK level is normal to slightly elevated during an attack.

Between attacks, the serum potassium level is usually in the upper normal range and the urinary potassium level is normal.

During an attack, EMG studies of paralyzed muscle show electrical silence. Between attacks, the EMG finding in the most common mutation is normal, while myotonia is seen in the less-common mutation. In myotonia, insertion of the EMG needle into a muscle causes a train of rapid electrical discharges that have a falling amplitude and frequency and sound like a “dive-bomber” when heard on the EMG speaker. Myotonia is due to

increased excitability of muscle fibers from the channelopathy (sodium channels or potassium channels in other myotonic diseases), producing repetitive action potentials in individual muscle fibers.

Muscle histology may be normal or demonstrate nonspecific changes to muscle fibers. In patients who develop permanent myopathy, muscle fibers may show vacuolations in muscle fibers, focal myofibrillar degeneration, and central nuclei.

Since the gene for hyperkalemic PP is known, blood tests are available for detection of the most common mutations. However, the diagnosis is commonly made in a patient with periodic paralysis who has a dominant family history and transient elevation of serum potassium level during an attack.

### Principles of Management and Prognosis

Since most attacks are brief, many patients do not require any drug treatment. Some patients can abort or shorten an attack by consuming carbohydrates or performing mild exercise at the start of an attack. Patients with severe frequent attacks

may benefit from chronic administration of thiazide or acetazolamide diuretics, which lowers the serum potassium level.

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# 5 DISORDERS OF THE NEUROMUSCULAR JUNCTION

## Overview

In humans, all nerve-to-nerve, nerve-to-muscle, and peripheral sensory receptor-to-nerve communication occurs via synapses. An electrical signal traveling along a nerve axon is converted at a specialized nerve ending called a synapse. At the synapse the electrical signal triggers release of a neurotransmitter into the synaptic cleft. The neurotransmitter then crosses the synaptic cleft to attach to a specialized receptor that is part of an ionic channel, resulting in either local depolarization or hyperpolarization of the postsynaptic cell. When sufficient ionic channels have been stimulated by neurotransmitters, the postsynaptic cell either completely depolarizes or becomes inhibited from depolarizing. In summary, all neural communication results from electrical-to-chemical-to-electrical transmission.

There are at least 30 different types of neurotransmitters, with the greatest number occurring in the CNS. In simple terms, neurotransmitters are classified into simple chemicals (acetylcholine, norepinephrine, and dopamine), amino acids (GABA, glycine, and glutamine), or peptides (substance P and endorphins). The duration of the neurotransmitter effect may be milliseconds, as in a brief opening and closing of an ionic channel, to

hours or days, as when a receptor stimulates intracellular second messengers that enzymatically affect intracellular pathways.

Synaptic disorders may occur from chemical or biologic toxins, antibodies directed against synaptic receptor molecules, or genetic mutations in the synaptic receptor or membrane channel. Synaptic disorders due to mutations in calcium, potassium, and sodium ion channels (called channelopathies) are responsible for such episodic disorders as seizures, migraine-type headaches, ataxia, myotonia, and weakness from Lambert–Eaton syndrome.

Synaptic disorders often have several suggestive clinical features: (1) excessive inhibition or excitation of one transmitter pathway, (2) signs and symptoms that are episodic or fluctuate considerably, and (3) signs that increase with continuing firing of the synapse.

This chapter focuses on diseases that result from toxins and antibodies affecting the neuromuscular junction to produce weakness.

## *Myasthenia Gravis*

### Introduction

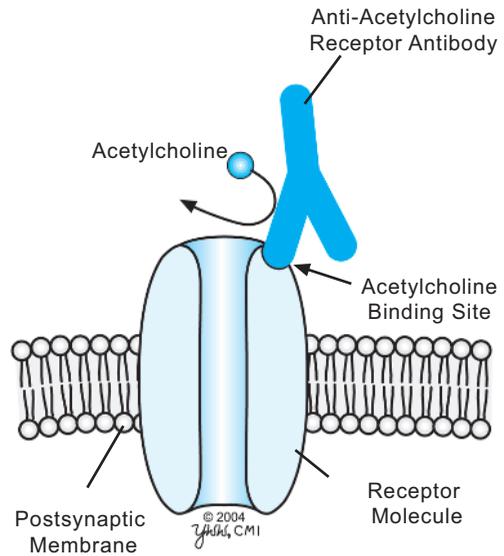
Myasthenia gravis (MG) is the most common disorder affecting the neuromuscular junction. MG is

not from a toxin; it originates from autoantibodies directed against the acetylcholine receptor (AChR). There are over 30,000 individuals with MG in the United States, with a prevalence of 10/100,000 adults. The epidemiology of MG demonstrates 2 peaks. The first peak, mainly in women, occurs between ages 10 and 40 years. The second peak has a male predominance and occurs from ages 50 to 75 years.

MG is considered the classic humoral autoimmune disease, based on well-characterized autoantibodies and the observation that these patients frequently develop other autoimmune diseases such as thyrotoxicosis, rheumatoid arthritis, and systemic lupus erythematosus.

### Pathophysiology

The etiology or initial event that begins the onset of MG remains unknown. However, the weakness results from 3 factors. The most important one is circulating antibodies directed against the AChR on the postsynaptic membrane of the neuromuscular junction. Some of these antibodies attach to the AChR located on key parts of the sodium/potassium channel, thereby interfering with opening the sodium/potassium channel (Figure 5-1). When sufficient AChRs are blocked by antibodies, the muscle will not depolarize sufficiently to trigger contraction of the muscle fiber. A second factor contributing to the weakness is that AChR molecules have a faster rate of degeneration. When AChR antibodies simultaneously attach to two adjacent AChRs, a cell signal initiates internalization of both receptors and degrades them. The turnover rate is faster than replacement of new membrane AChRs, resulting in a net loss of available AChRs at the synapse. The third factor develops because the antibody attached to the AChR triggers serum complement activation, producing secondary damage to the synaptic membrane. As a consequence of years of complement damage, the postsynaptic membrane loses its rich invaginations and becomes simplified in structure (Figures 5-2a and 5-2b). In severe chronic cases, the postsynaptic membrane may have a 2/3 reduction in the normal number of AChR molecules, a number insufficient to initiate depolarization and contraction of the muscle fiber even if no acetylcholine antibodies were present. In these patients, pyridostigmine usage does not improve the probability of muscle fiber contraction.



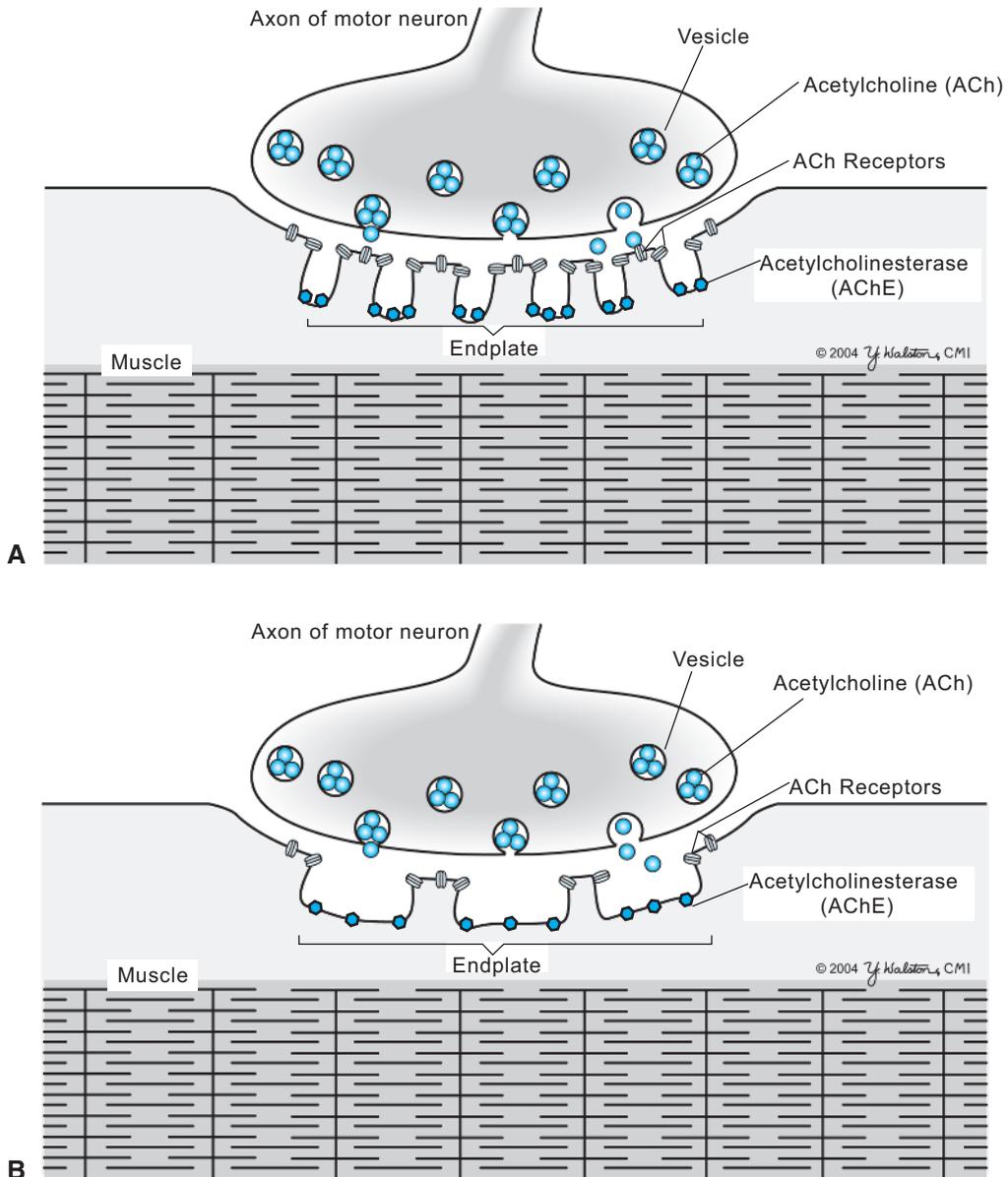
**Figure 5-1** In myasthenia gravis, acetylcholine receptor antibody blocks the acetylcholine-binding site.

Of these patients, 75% have an associated abnormality of the thymus gland. About 85% of these patients have thymic hyperplasia with germinal center lymphocyte proliferation, and 15% have a thymoma. The role of the thymus gland in producing the abnormal antibodies is poorly understood. The current hypothesis is that the AChR antibody is a T-cell-mediated antibody response. Surgical removal of the thymus gland often results in clinical improvement and a reduction of the number of circulating antibodies.

MG can occur in infants. Infants born to mothers with MG may have sufficient circulating antibodies to cause the infant to become floppy, weak, and have a poor suck. This transient syndrome lasts for several weeks until the maternal antibody disappears. Other infants have congenital MG that is due to genetic mutations in the AChR. These infants remain persistently weak and do not respond to immunosuppressive drugs.

### Major Clinical Features

Clinical features result from blockade at the neuromuscular junction and affect skeletal muscles in a fluctuating and fatigable manner (Table 5-1). The disease usually has a subacute onset. Earliest symptoms are ptosis and diplopia. Patients complain of droopy eyelids and double vision that



**Figure 5-2** Neuromuscular junction. (a) Normal. (b) Myasthenia gravis with simplified postsynaptic membranes.

varies during the day and worsens as the day progresses. In 15% of patients, the disease does not progress beyond ocular problems. For most other patients, other signs of bulbar muscle weakness appear, with trouble chewing, swallowing, and speaking loudly. Some patients find they eat their big “dinner” meal for breakfast as they have trouble chewing meat by the end of the day. Limb weakness is common and affects proximal muscles

to a greater extent than distal muscles. Although brief maximal muscle testing may appear normal, patients often cannot hold their arms outstretched for even a minute without fatigue. In severe cases, patients cannot walk and develop respiratory weakness. Sensation, mentation, and deep tendon reflexes are not affected.

Maximal weakness appears within the first 3 years of clinical onset. About 10% of patients

**Table 5-1 Cardinal Features of Myasthenia Gravis**

Weakness
<ul style="list-style-type: none"> <li>• Bulbar muscles: ptosis, diplopia, dysarthria, dysphagia, and chewing difficulty</li> <li>• Limb muscles: proximal greater than distal weakness</li> </ul>
Fatigability of skeletal muscles
<ul style="list-style-type: none"> <li>• Increased weakness in afternoon or after exercise</li> </ul>
Normal mentation, sensation, and deep tendon reflexes

experience a spontaneous remission, which occurs within the first 2 years. However, the remainder of patients have a life-long chronic illness that fluctuates in severity.

### Major Laboratory Findings

Serum antibodies directed against the AchR are found in over 85% of patients. A few additional MG patients have a blocking antibody. The level of antibody titer does not always reflect disease severity, as the test detects all AchR antibodies, including those that do not interfere with the functioning of the channel. However, for a given patient, a falling titer does reflect clinical improvement.

X-ray or CT of the chest may demonstrate a thymoma. Elevated thyroxin blood levels indicating thyrotoxicosis are found in up to 5% of patients.

Repetitive nerve stimulation (at rate of 3/s) of proximal muscles (often the trapezius muscle) usually demonstrates a decremental fall of greater than 15% in the compound muscle action potential (see Chapter 3, “Common Neurologic Tests”).

The tensilon test, which can be performed in the office, is helpful for establishing the diagnosis of MG when there are clear ocular signs. Edrophonium (Tensilon®) is a brief-acting anticholinergic drug that is slowly given intravenously to a patient. For the next 5 to 10 minutes, an untreated MG patient should have a clear objective improvement in ptosis. Often a saline injection precedes the administration of edrophonium to evaluate for a placebo effect.

### Principles of Management and Prognosis

The goal of treatment is to improve strength and to reduce or eliminate circulating antibodies against the AchR. Symptomatic treatment aimed at improving strength is accomplished with anticholinesterase drugs. These drugs do not reduce circulating antibody titers, but are the first line to improve the patient’s strength. Pyridostigmine (Mestinon®) is the main oral drug; it is given to the patient several times a day. Anticholinergic medications act by interfering with acetylcholine esterase, the enzyme that cleaves acetylcholine in the synaptic cleft. Partial inhibition of this enzyme results in a longer time period that acetylcholine molecules can remain in the synaptic cleft to find unblocked AchR and increase the probability that sufficient AchR channels will open to fully depolarize and contract the muscle fiber. Too much pyridostigmine, however, can block all the acetylcholine esterase such that acetylcholine cannot be cleaved and removed once it attaches to an AchR. The inability to remove acetylcholine from the receptor causes a depolarizing muscle weakness that is called a “cholinergic crisis.”

A number of treatments are aimed at reducing the amount of circulation antibody. Thymectomy, the surgical removal of the thymus gland, in a moderately severe patient often results in clinical improvement and a fall in antibody titer. Corticosteroids and other immunosuppressive drugs (azathioprine and cyclosporine) are commonly given to lower the antibody titer and improve strength. IVIg and plasma exchange by plasmaphoresis will temporarily reduce circulating antibody and improve strength for several weeks. These temporary methods can be used for patients requiring prompt clinical improvement such as for elective surgery, pneumonia, or a “myasthenic crisis.”

Patients with MG should avoid drugs such as aminoglycoside antibiotics, chloroquine, and anesthetic neuromuscular–blocking drugs (pancuronium and D-tubocurarine), which affect the neuromuscular junction.

Using various combinations of pyridostigmine and immunosuppressants to lower circulating antibody levels, most patients lead fairly normal lives. Death is now uncommon and generally develops from pneumonia or acute respiratory failure.

## Botulism

### Overview

Toxins have long been recognized as having the ability to affect the neuromuscular junction, resulting in paralysis or muscle spasms. Drugs such as curare are known to block the postsynaptic excitatory AchRs in the peripheral nervous system, producing paralysis. Hyperexcitable states result from intoxication with tetanus toxin or lysergic acid diethylamide (LSD). Tetanus toxin blocks the inhibitory glycine receptor between the spinal cord Renshaw cell and the anterior horn cell. Lack of inhibition on anterior horn neurons causes them to repeatedly fire upon minor excitation, producing profound muscle spasms. LSD appears to cause profound hallucinations by interfering with CNS serotonin synaptic receptors.

Botulinum toxin is the most potent biologic toxin known. The 50% lethal dose ( $LD_{50}$ ) for humans has been calculated to be 0.1  $\mu\text{g}$  for intravenous or intramuscular inoculation (wound botulism), and 70  $\mu\text{g}$  for oral exposure (foodborne botulism). Botulism is a descending, symmetric,

flaccid paralysis due to interrupted transmission of peripheral motor and cholinergic autonomic nerves at their synapses. Human disease occurs mainly from consumption of preformed botulinum toxin (foodborne botulism) and growth of *Clostridium botulinum* in the gastrointestinal tract of infants with subsequent absorption of the toxin (infant botulism). However, cases of wound botulism are increasing primarily in heroin addicts who subcutaneously (“skin popping”) inoculate *C. botulinum* spore-contaminated heroin (Figure 5-3).

The incidence of botulism varies by type. About 1,000 cases of foodborne botulism are reported annually around the world and about 32 cases annually in the United States. About 40 cases/yr of wound botulism are reported mainly from southwestern states as a consequence of the use of Mexican black tar heroin contaminated with *C. botulinum* spores. Nearly 70 cases/yr of infant botulism occur in the United States.

### Pathophysiology

The bacterium *C. botulinum* is a spore-forming anaerobic gram-positive bacillus that is com-

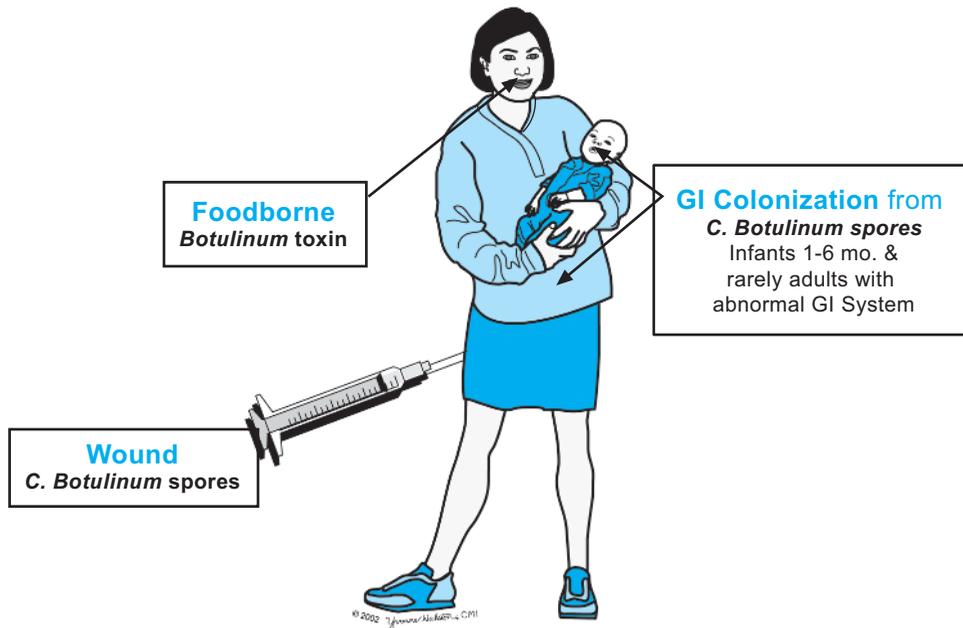


Figure 5-3 Types of botulism.

monly found in soil and water sediment around the world. *C. botulinum* produces 7 types of neurotoxins; humans are intoxicated mainly by types A, B, or E.

Botulinum toxin is an odorless and tasteless 150-kd molecule that is comprised of a heavy chain (100 kd) and a light chain (50 kd) held together by a disulfide bond (Figure 5-4). In foodborne botulism, the toxin is protected from stomach acid by other proteins released by *C. botulinum* that loosely attach to the toxin. In the upper intestine, the toxin is actively transported through intestinal lining cells by receptor-mediated transcytosis (crossing the cells as an intact molecule via a vesicle). Upon reaching the bloodstream, toxin circulates until it reaches a peripheral acetylcholine synapse. The toxin does not cross the blood–brain barrier, so it does not affect brain cholinergic synapses. The heavy chain possesses a highly specific domain that attaches to the presynaptic side of the synapse (Figure 5-5). The toxin is then internalized into the cytoplasm via an endocytotic vesicle. As the pH within the vesicle lowers, the toxin reconfigures and the heavy chain penetrates the vesicle wall, allowing the light chain to pass through the vesicle wall and release into the cytoplasm. The light chain, a zinc-containing endopeptidase enzyme, subsequently cleaves docking proteins called soluble *N*-ethylmaleimide–sensitive factor attachment protein receptor (SNARE) proteins. SNARE proteins enable vesicles containing quantal amounts of acetylcholine to fuse with the presynaptic membrane to release acetylcholine into the synaptic cleft. Thus, botulinum toxins block stimulus-induced and spontaneous quantal acetylcholine release on the presynaptic side of the cholinergic

synapse. As a consequence of the light chain cleaving SNARE proteins, the muscle fails to contract and the cholinergic parasympathetic nerve fails to function. The resulting synaptic failure continues for weeks to 6 months. The high potency of botulinum toxin results from its high specificity to attach to only a few membrane sites and the fact that the toxin is an enzyme that cleaves critical proteins needed for synaptic function.

Clinical recovery occurs over 2 to 3 months and is due to terminal sprouting, where the incoming axon at the paralyzed neuromuscular junction sends a new branch to the same muscle fiber, forming a new synapse, or by the neuronal cell body producing new SNARE proteins and sending them by axoplasmic flow to the distal terminal.

The pathophysiology of infant botulism is unique in that the disease results from growth of *C. botulinum* in the gut with production of toxin rather than consumption of the preformed toxin. Infant botulism occurs in children only during the first 12 months of life, with a peak at 2 to 3 months. After that age, the normal gastrointestinal (GI) tract will not allow colonization of *C. botulinum*. The infant consumes *C. botulinum* spores by eating dust, honey, or other food substances that contains spores. In the immature gut, the spores germinate, colonize, and produce botulinum toxin, which is slowly absorbed.

## Major Clinical Features

### FOOD-BORNE BOTULISM

After ingestion, the mean incubation period is 2 days, with a range from 0.5 to 6 days. The longer the incubation period, the milder the symptoms. Botulism classically presents with symmetric, descending flaccid paralysis with prominent bulbar palsies in an afebrile patient with a normal sensorium. Prominent bulbar palsies include diplopia, external ophthalmoplegia, dysarthria, dysphonia, dysphagia, and facial weakness. Blurry vision from paresis of accommodation and diplopia from CN VI palsy are early signs. Limbs become weak over 1 to 3 days and may become completely paralyzed. Deep tendon reflexes become depressed or absent. Weakness of respiratory muscles develops and may be severe enough to require intubation and mechanical ventilation. Smooth muscle paralysis typically involves consti-

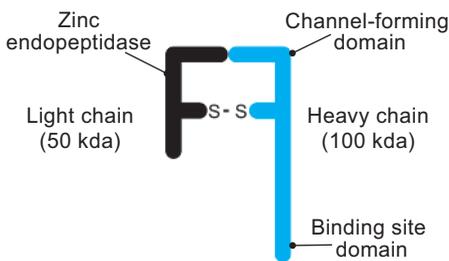
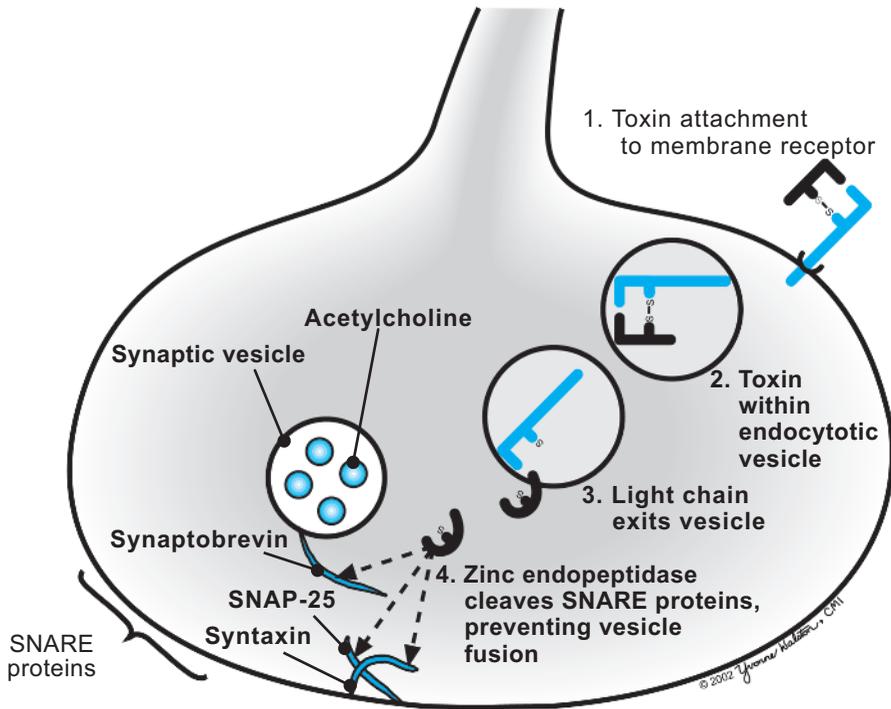


Figure 5-4 Botulinum toxin.



**Figure 5-5** Action of botulinum toxin at the synapse.

pation, paralytic ileus, and urinary retention. In *wound botulism*, the clinical picture is similar.

#### INFANT BOTULISM

Infants develop an illness that progresses over hours to 20 days (mean 4 days) that is characterized by constipation (no defecation for 3 or more days), lethargy, hypotonia (floppy infant), poor cry, poor feeding, and loss of head control.

#### Major Laboratory Findings

The CSF and blood typically are normal. The clinical diagnosis is made on a characteristic clinical picture and abnormal nerve studies. Nerve conduction studies show widespread low-amplitude compound muscle action potentials with normal distal latencies, conduction velocities, and sensory nerve action potentials. If the nerve receives 10 seconds of fast repetitive electrical stimulation (30–50 Hz), there is an increment in the compound muscle action potential amplitude secondary to increased release of acetylcholine quanta.

The definitive diagnosis is the demonstration of botulinum toxin in serum, stool, or suspected food or isolation of *C. botulinum* from a wound site. The most sensitive diagnostic test for the presence of botulinum toxin is a biologic test involving mice. These tests are positive in about  $3/4$  of clinically diagnosed cases.

#### Principles of Management and Prognosis

Treatment should begin promptly after there is a suspicion of botulism or after a clinical diagnosis is made. Aims of treatment are to (1) support respiration, (2) prevent progression of the paralysis by use of antitoxin, and (3) prevent pulmonary or other complications until spontaneous recovery occurs.

Weakness and respiratory failure may rapidly progress within hours. Patients should be hospitalized in an intensive care unit with careful monitoring of respiratory function. Intubation and mechanical ventilation is required in over  $1/2$  of patients. Use of a ventilator averages about 2 weeks but can be as long as 2 months.

State health officials should be immediately notified to bring antisera and to help should there be additional cases, as seen in a common source outbreak of foodborne botulism. For botulism in adults, administration of equine trivalent (types A, B, and E) botulism antitoxin should be as soon as possible without waiting for laboratory confirmation. The antitoxin eliminates circulating toxin but does not remove toxin that has already entered the neuromuscular junction. Therefore, the antitoxin will not reverse paralysis that has occurred but will prevent progression of the weakness and may shorten hospitalization. Each 10-mL vial sufficiently neutralizes circulating toxin found in all forms of botulism. Because the antitoxin is produced in horses, there is a 3% incidence of allergic reactions, including anaphylaxis. In infant botulism, human botulinum antitoxin—human Botulinum Immune Globulin-IV (BIG)—is available; it has similar effects, but eliminates the administration of a for-

eign protein. Use of BIG has been shown to shorten the time on a ventilator and hospitalization.

Excellent nursing care will minimize complications. Yet despite everything, the mortality rate is 5% to 15%. Patients who survive will regain normal muscle strength but often complain of fatigue for years.

## RECOMMENDED READING

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- Cherington M. Clinical spectrum of botulism. *Muscle Nerve* 1998;21:701–710. (Good review of the clinical types of botulism.)
- Drachman DB. Myasthenia gravis. *N Engl J Med* 1994;330:1797–1810. (Excellent overall review.)
- Simpson LL. Botulism toxin: potent poison, potent medicine. *Hosp Pract* 1999;34:87–91. (Excellent recent review of the mechanism of action of botulinum toxin.)

## 6 DISORDERS OF PERIPHERAL NERVES

### Overview

The peripheral nervous system (PNS) involves all nerves lying outside the spinal cord and brainstem except the olfactory and optic nerves, which are extensions of the CNS itself. All peripheral nerve axons are invested either with a wrapping of myelin made by Schwann cells (myelinated nerves) or by cytoplasm of Schwann cells (unmyelinated nerves). This chapter will focus on motor and sensory nerves and excludes the sympathetic and parasympathetic nerves.

The entire peripheral nerve divides into three compartments. Between each spinal cord level and the corresponding dorsal root ganglion (DRG), motor and sensory fibers separate into dorsal or ventral roots. Distal to the dorsal root ganglion, sensory and motor fibers combine. Those nerves innervating limbs travel to the brachial or lumbar plexus. In the plexus, sensory and motor nerve axons separate and recombine to form specific peripheral nerves. Peripheral nerves carry motor, sensory, or autonomic fibers, often in a mixture with a 2:3 ratio of myelinated to unmyelinated fibers.

Although a few peripheral nerves contain only sensory fibers (e.g., sural nerve) or motor fibers (vagus nerve to diaphragm), most peripheral nerves have their own territory of skin and specific

muscles. Each spinal cord root innervates a defined area of skin sensation (dermatome) (see Chapter 2, Figure 4) and a defined group of muscles (myotome) that differs from the innervation of a specific nerve. Knowledge of the differences helps determine the location of a lesion (root, plexus, or peripheral nerve).

Peripheral nerve diseases are traditionally classified in different ways such as motor, sensory, or mixed nerve diseases; polyneuropathy (multiple nerve involvement that is usually distal) versus mononeuropathy (single nerve involvement); and demyelinating versus axonal diseases. Demyelinating peripheral nerve disease is also discussed in Chapter 10, “Disorders of Myelin.”

### Pathophysiology

Peripheral nerve damage occurs by 6 basic mechanisms: (1) axon transection, (2) axon compression (compression neuropathy), (3) neuron death, (4) metabolically sick neurons unable to support the distal axon (“dying-back” neuropathy), (5) demyelination, and (6) synapse dysfunction.

Following transection or severe compression, the axon distal to the injury degenerates (wallerian degeneration) over a period of a few weeks.

However, the axon segment proximal to the lesion does not. The sensory territory of the nerve is lost and the muscles innervated by the peripheral nerve become weakened or paralyzed.

A motor unit, defined as the lower motor neuron and all of its muscle fibers, may contain 10 to 1,000 muscle fibers. Each muscle fiber receives innervation from only one motor neuron. Following loss of motor neurons, muscle fibers become paralyzed. After about 10 days the muscle fiber undergoes biochemical changes as the neuromuscular junction degenerates. The muscle then acquires AchRs diffusely instead of only at the synapse. These new AchRs make the muscle supersensitive, and spontaneous depolarization can be detected when a needle electrode passes into the involved fiber (fibrillations and positive sharp waves). The muscle fiber undergoes atrophy and may involute to  $\frac{1}{3}$  of the original size.

If the neuron becomes metabolically sick, the nerve can no longer maintain the most distal part of its axon. The distal motor and sensory axons slowly degenerate (dying-back neuropathy). The longer the axon length, the more susceptible the nerve to metabolic damage. As a consequence, symptoms (often sensory loss) develop first in the toes (the longest axon).

Peripheral nerve myelin damage occurs from death of the attached Schwann cell and from immune attack or degeneration of the myelin sheath. The loss of myelin, usually in segments (segmental demyelination), interrupts transmission of sensory or motor signals, producing symptoms. The cause of the myelin damage may be genetic (hereditary sensorimotor neuropathy or Charcot-Marie-Tooth disease), autoimmune (Guillain-Barré syndrome), toxic (lead), or infectious (leprosy).

Synapse dysfunction interrupts the ability of the peripheral nerve to communicate with its target muscle or autonomic organ (see Chapter 5, “Disorders of the Neuromuscular Junction”). The result is weakness (myasthenia gravis) or paralysis (botulism) plus a variety of autonomic dysfunctions (hypotension, trophic skin changes, loss of sweating, etc.).

Unlike the CNS, the PNS recovers following damage. Mechanisms of recovery include (1) spontaneous recovery of axons, (2) regeneration of nerve axons, (3) axonal sprouting of intact adjacent axons, and (4) remyelination. If the entrapment or crush injury is not severe and the cause corrected, the existing axons recover over minutes

to weeks. Following nerve transection or severe crush injury, the proximal axons grow outward, provided the nerve sheath remains intact, at about 1 mm/day, so months are required before the return of strength or sensation occurs. Following death of the motor neuron, the now “orphaned” muscle fibers generate an unknown trophic factor that triggers adjacent motor axons to undergo segmental demyelination. This segment sprouts a branch axon that reinnervates the muscle fiber, making it part of a new motor unit.

## Clinical Features

Clinical features indicative of peripheral nerve disease are listed in Table 6-1.

## Diabetic Distal Symmetrical Polyneuropathy

### Introduction

Peripheral neuropathy is common, with a prevalence of about 2.5% in adults, rising in the elderly to almost 8%. The myriad causes include metabolic disturbances (diabetes mellitus and uremia), toxins (alcohol, cisplatin, and arsenic), vitamin deficiencies (B12 and B2), genetic (hereditary sensorimotor neuropathy and porphyria), immune-mediated illness (Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy), vasculitis (rheumatoid arthritis, Sjögren’s syndrome, and polyarteritis nodosa), and neoplastic disorders (lymphoma, multiple myeloma, and paraneoplastic neuropathy). Diabetic neuropathy accounts for over  $\frac{1}{2}$  of all causes.

Diabetes mellitus affects more than 100 million people worldwide. Diabetic neuropathy, present in about 10% of patients at the time of diagnosis, rises to over 50% when the diabetes has been present for years. While diabetes causes several types of peripheral nerve disease, distal peripheral polyneuropathy accounts for over 90% of cases.

### Pathophysiology

The pathogenesis of diabetic neuropathy, while multifactorial, likely stems from persistent hyperglycemia. At the nerve cell body located in the dor-

**Table 6-1 Clinical Features that Suggest Peripheral Nerve Diseases**

<b>Specific Peripheral Nerve Damage</b>
<ul style="list-style-type: none"> <li>• Both sensory loss and muscle weakness are present.</li> <li>• Sensory loss and muscle weakness occur in the territory of the peripheral nerve.</li> <li>• Involved muscles atrophy after a month down to 1/3 of their former size.</li> <li>• Sensory changes cause loss of pain, touch, temperature, vibration, and position sense if the lesion is destructive or produce pain or paresthesias if the lesion is irritative.</li> <li>• Diminished or loss of tendon reflex corresponds to the involved nerve.</li> <li>• Secondary trophic skin changes may slowly develop from the lack of autonomic nerve innervation.</li> <li>• Onset may be acute or gradual depending on etiology.</li> <li>• Involvement is unilateral and seldom bilaterally symmetrical, although multiple nerves may be involved (mononeuritis multiplex).</li> </ul>
<b>Distal Symmetrical Polyneuropathy or “Dying-Back” Neuropathy</b>
<ul style="list-style-type: none"> <li>• Maximum loss of sensation should be in toes and feet.</li> <li>• Sensory and motor loss should be symmetrical.</li> <li>• Onset is gradual and not acute.</li> <li>• Loss of sensation is usually greater than loss of strength.</li> <li>• Painful dysesthesias may occur mainly in the feet.</li> <li>• Fingers lose sensation when the leg neuropathy advances to about the knee.</li> <li>• Muscle loss in the feet usually begins as “hammer toes” or pulling back of toes dorsally due to weakness of flexor intrinsic foot muscles without corresponding weakness of extensor muscles located in the leg.</li> <li>• Trophic changes in the foot and nails are common from loss of autonomic nerves.</li> </ul>
<b>Demyelination of Peripheral Nerves</b>
<ul style="list-style-type: none"> <li>• Major finding is weakness, with minimal loss of myelinated sensory fibers for vibration and position sense.</li> <li>• Weakness is usually bilateral and symmetrical.</li> <li>• Pain, touch, and temperature sensations are preserved.</li> <li>• Onset may be abrupt (Guillain-Barré syndrome), subacute (lead), or gradual (hereditary sensorimotor neuropathy).</li> </ul>

sal root ganglion there is cellular injury, leading to impaired protein and lipid synthesis and impaired axonal transport. At the distal end of the nerve, due to the impaired transport, there is nerve degeneration. The degeneration is exacerbated by the loss of skin trophic support. So the nerve initially (over a period of many years) becomes dysfunctional in a distal-to-proximal fashion but in severe cases there is total nerve loss. Other proposed pathogenic mechanisms include (1) hyperglycemia-induced increases in polyol pathway activity, with accumulation of sorbitol and fructose in nerves and secondary axonal damage, (2) microvascular disease of peripheral nerves, leading to nerve ischemia and hypoxia, (3) increased glycosylation of proteins critical to neuronal function, (4) reduction in expression or binding of neurotrophic factors, and (5)

impaired detoxification of reactive oxygen species that then mediate nerve damage.

Diabetic nerves examined from biopsies or autopsies demonstrate damage to both myelinated and unmyelinated axons that is more pronounced distally than proximally. In addition, local vascular disease within the perineurium includes basement membrane thickening, endothelial cell proliferation, and vessel occlusions.

### Major Clinical Features

This insidious syndrome initially affects the toes bilaterally and symmetrically. Here the loss of small unmyelinated axons diminishes appreciation of pain and temperature. As axon loss progresses to involve the foot and then the lower leg, the

numbness ascends with it. Because of the inability to appreciate pain, injuries of the foot and ankle can lead to secondary foot ulcers and traumatic arthritis of joints (Charcot joints). Often the patient remains unaware of the loss of sensation in the feet until secondary foot or ankle problems develop. When the neuropathy has marched to the knees, the patient usually notes loss of sensation in the fingertips (Figure 6-1).

In 10% of patients with diabetic polyneuropathy, damage to small axons leads to persistent foot pain. The pain, typically described as burning, constant, prickling, and painful to light touch (allodynia), may be so uncomfortable that the patient seeks medical attention.

Large, sensory, myelinated axon damage with subsequent loss of vibration and position sense in toes and feet produces gait and balance problems. Motor nerve axons may be involved with weakness of intrinsic foot muscles.

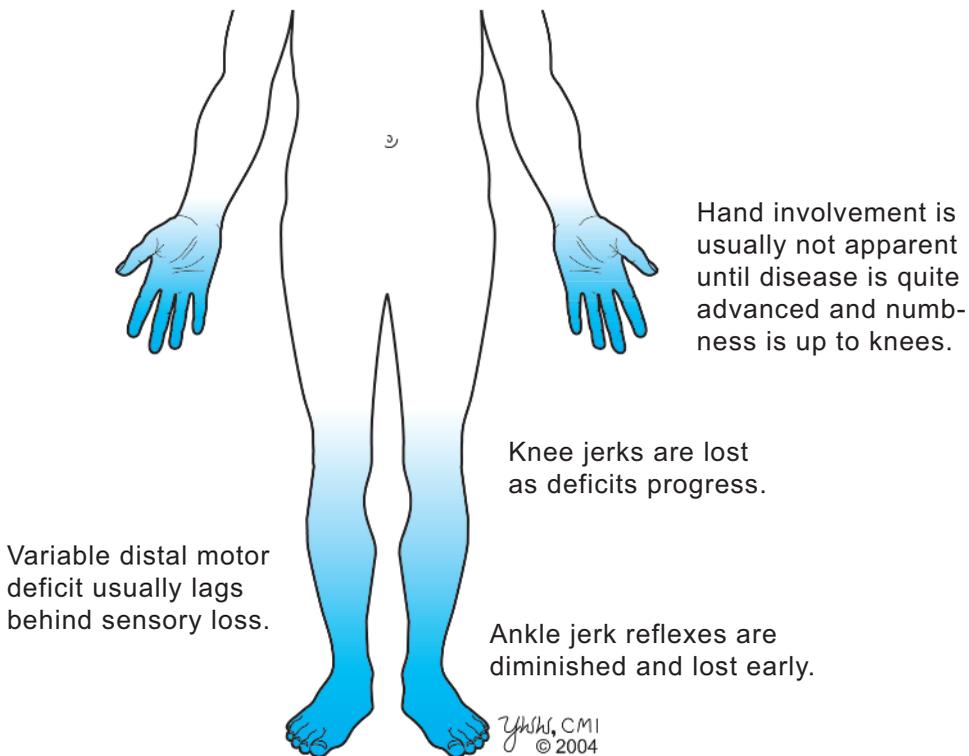
Autonomic nerve axons are also impaired, leading to loss of sweating, thinning of involved skin,

asymmetrical pupils that poorly accommodate to darkness, erectile dysfunction, loss of ejaculation, constipation and/or diarrhea, and orthostatic hypotension.

**Major Laboratory Findings**

Since the neuropathy begins distally in the feet and involves unmyelinated axons, nerve conduction studies of sensory and motor nerves of the leg may initially show mild changes, as electrophysiologic studies seldom detect abnormalities in unmyelinated axons. As the neuropathy progresses, the findings of axonal degeneration predominate, with diminished amplitude of compound muscle action potentials and sensory nerve action potentials. Needle electromyography of intrinsic foot muscles shows denervation potentials. There is relative preservation of proximal conduction velocities.

A nerve biopsy, while seldom performed, shows nonspecific axonal damage to both myelinated and unmyelinated axons. A nerve biopsy should come



**Figure 6-1** Peripheral polyneuropathy distribution.

from a sensory nerve (like the sural nerve) that has a small area of sensory innervation. Biopsy of a mixed nerve will lead to paralysis of innervated muscles and thus is performed only on an intercostal nerve.

Skin-punch biopsy (3–4 mm full-thickness biopsy) with immunohistochemical staining for peripheral nerve axons is becoming more popular. The histologic sections demonstrate marked reduction in the density of epidermal nerve fibers that is helpful, but not diagnostic, for diabetic neuropathy. Thus the diagnosis relies mainly on the clinical history and neurologic examination of the feet and lower legs.

### Principles of Management and Prognosis

The management of diabetic neuropathy can be divided into preventing progression of the neuropathy, minimizing problems from anesthesia of feet and hands, and reducing burning foot pain.

Numerous studies demonstrate that good control of blood glucose can slow, halt, or reverse progression of the neuropathy. Glucose control involves weight loss, exercise, and use of hypoglycemic agents.

Foot anesthesia predisposes this limb to ulceration and infection. Proper footwear minimizes foot and ankle trauma. The individual should be instructed to inspect their feet regularly for signs of infection or ulceration and to place their hand in shoes to detect objects in the soles. If loss of position sense in the feet declines, the patient should use night-lights and caution when walking on uneven surfaces or in the dark.

Treating the patient with a painful peripheral neuropathy is a challenge. For many patients, the pain is reduced with tricyclic antidepressants (amitriptyline and nortriptyline) in low doses. Anticonvulsants, such as gabapentin or carbamazepine, may be slowly added if the pain relief is insufficient. In some patients, foot pain spontaneously subsides when the sensory neuropathy progresses to anesthesia.

## Carpal Tunnel Syndrome

### Introduction

Carpal tunnel syndrome (CTS) is an example of compression mononeuropathy. Up to 15% of individuals experience occasional symptoms suggestive of CTS. However, the prevalence of

electrophysiologically confirmed, symptomatic carpal tunnel syndrome is 3% in women and 2% in men, with peak prevalence in older women. Fortunately, few individuals develop sufficient signs and symptoms to require surgical treatment.

### Pathophysiology

Elevated pressure in the carpal tunnel produces CTS (Figure 6-2a). The increased pressure causes ischemia of the distal median nerve, resulting in impaired nerve conduction with paresthesias and pain along the nerve distribution. Early in the clinical course there are no morphologic changes in the median nerve and the symptoms are reversible. However, as compression progresses with prolonged ischemia, axonal injury and nerve dysfunction become permanent.

About 1/3 of patients have associated conditions such as pregnancy, inflammatory arthritis, Colles' fracture, amyloidosis, hypothyroidism, diabetes mellitus, and use of corticosteroids or estrogens. The remaining 2/3 have their CTS associated with repetitive, often forceful, activities of the hand and wrist.

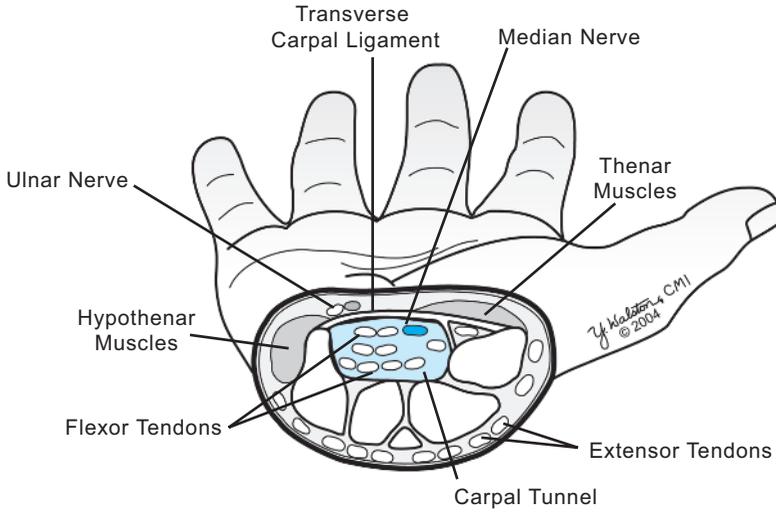
### Major Clinical Features

The symptoms and signs of CTS correspond to the distribution of the distal median nerve (Figure 6-2b). Patients usually complain of pain, tingling, burning, and numbness that involve the palmar aspect of the thumb, index finger, middle finger, and often the radial half of the ring finger. The fifth digit is only occasionally involved. The symptoms, often worse at night, may awaken the individual with hand discomfort extending into the lower arm that causes the individual to shake their hand ("flick sign"). Symptoms tend to be worse following a day of increased repetitive activity and often increase with driving.

Early, clinical exam shows normal sensation in the hand and no weakness or atrophy of median nerve-innervated muscles. As the disease advances, two-point discrimination in median nerve distribution (finger tips) diminishes and atrophy occurs in the thenar muscles (oppones pollicis and abductor pollicis brevis).

Helpful, but not diagnostic, bedside tests include Phalen and Tinel signs. In Phalen's maneuver, the patient reports that flexion of the wrist for

**A**



Median Nerve at Carpal Tunnel

**B**

Distribution of Median Nerve

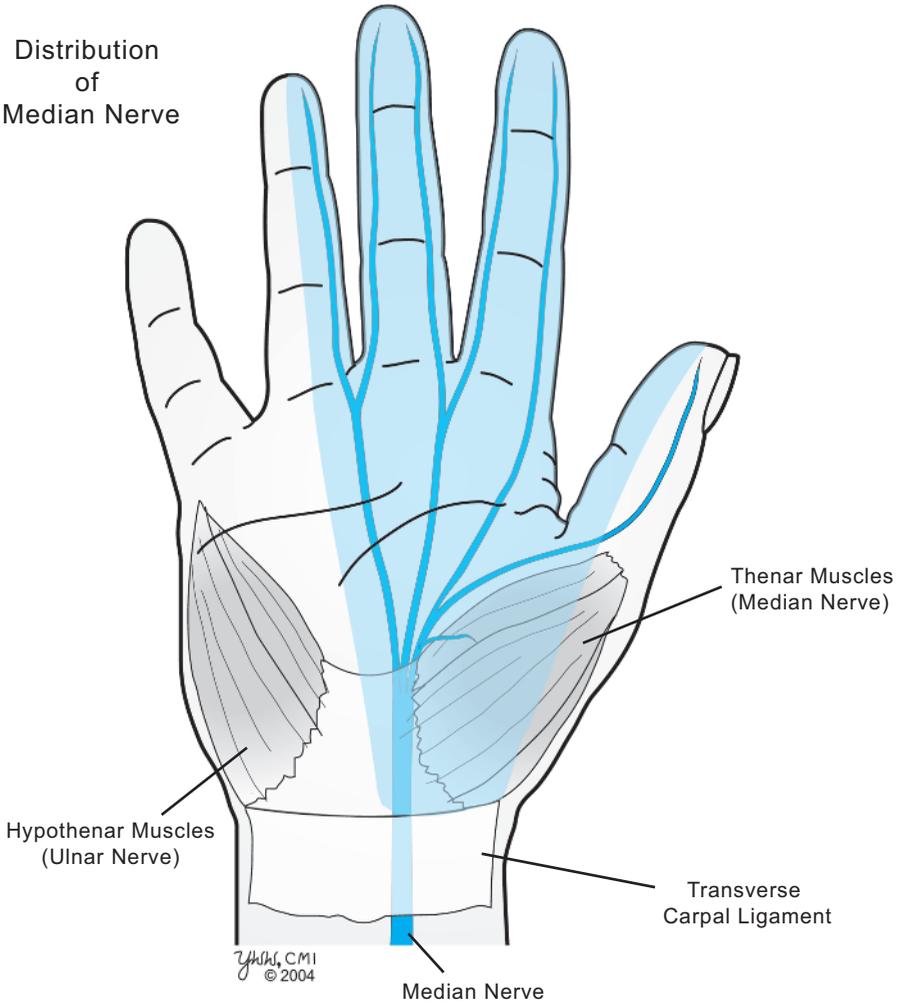


Figure 6-2 Median nerve. (a) Carpal tunnel syndrome. (b) Sensory distribution.

60 seconds elicits pain or paresthesias in the median nerve distribution. Tinel's sign occurs when lightly tapping the volar surface of the wrist causes radiating paresthesias in the first 4 digits. For both tests, the sensitivity is about 50% but the specificity is slightly higher.

### Major Laboratory Findings

Abnormal delay of median nerve sensory latency across the wrist is the major laboratory test that confirms the clinical diagnosis. If median nerve axonal loss occurs, the electromyogram of thenar muscles may show evidence of denervation.

### Principles of Management and Prognosis

When CTS arises from other medical conditions, treatment of the underlying condition often improves the symptoms. Thus, administration of thyroid in the patient with hypothyroidism, use of antiinflammatory drugs for wrist arthritis, and delivery of a pregnancy will improve symptoms. Similarly, reduction of the triggering repetitive wrist movement may improve symptoms.

Use of a wrist splint that holds the wrist in the neutral position helps symptoms in many patients. Wearing the splint at night may improve symptoms within a week. Nonsteroidal antiinflammatory drugs often prove to be of little benefit. Local injections with lidocaine and long-acting corticosteroids into the carpal tunnel can give striking relief, but symptoms return after weeks or months in 60% of the cases. Injections can be repeated a total of 3 to 4 times. Surgery is usually recommended to patients developing objective sensory or motor axonal loss of the median nerve. The surgeon usually releases the transverse carpal ligament (roof of the carpal tunnel) (Figures 6-2a and 6-2b) under direct visualization or through an endoscope. Over 3/4 of patients experience pain relief within days after surgery, but full use of the hand may take several weeks.

## Bell's Palsy

### Introduction

Bell's palsy or idiopathic peripheral facial nerve palsy is the most common cause of CN VII dysfunction. The facial nerve contains around 10,000 axons, of which 70% are motor nerves (special vis-

ceral efferent) that innervate muscles of the face. The remaining fibers include general visceral efferent nerves that are parasympathetic nerves to the lacrimal and submandibular glands—special visceral afferent nerves that represent taste from the anterior 2/3 of the ipsilateral tongue, and general somatic afferent nerves that transmit sensation from the skin of the ear pinna and external auditory canal. The facial nerve travels with the auditory nerve in the internal auditory canal and enters the facial canal, where it soon reaches the geniculate ganglion containing the neuronal cell bodies for taste and ear sensation. The greater petrosal nerve, the first branch, travels to the lacrimal gland. The second branch runs to the stapedius muscle, and the third branch—the chorda tympani nerve—travels to the tongue. The nerve exits the facial canal at the stylomastoid foramina, where it passes through the parotid gland and spreads out to innervate 23 facial muscles (but not the masseter and lateral and medial pterygoid muscles innervated by the trigeminal nerve).

Numerous diseases cause facial palsy in adults, including trauma (facial trauma and basal skull fracture), infections (Lyme disease, otitis media, syphilis, meningitis, and mumps), tumors (parotid tumors, sarcoma, and facial nerve meningioma), and brainstem disorders (multiple sclerosis and strokes). However, almost 60% of cases are considered idiopathic and due to Bell's palsy.

Bell's palsy occurs over 65,000 times a year, with an equal racial and sex distribution. Cases occur in all ages, but the incidence increases with age. It is rare for Bell's palsy to be bilateral or to recur.

### Pathophysiology

The pathogenesis of Bell's palsy remains poorly understood. MRI and pathologic studies show the facial canal, especially in the tympanic and labyrinthine segments, as the site of pathology. The nerve becomes edematous and may develop mild-to-moderate wallerian degeneration, with varying amounts of surrounding lymphocytic inflammation. The geniculate ganglion may appear normal or have inflammation. Early theories suggested ischemia to the facial nerve led to nerve edema and nerve compression from the walls of the facial canal. Later, the ischemia concept was dropped and the nerve edema was considered idiopathic. Recently, viral infection

theories have focused on varicella-zoster and herpes simplex viruses as potential viruses that reactivate in the facial nerve or geniculate ganglion to cause nerve damage, edema, and inflammation. While varying degrees of wallerian degeneration develop, all axons are rarely destroyed. As such, spontaneous recovery usually occurs.

### Major Clinical Features

The hallmark of Bell's palsy is the abrupt onset of painless unilateral complete or incomplete facial weakness (Figure 6-3). Since damage of the facial nerve occurs in the facial canal, other nerve branches are dysfunctional, with variable incidences. In 10% to 15% of patients, vesicles appear on the skin of the ipsilateral ear pinna, external auditory canal, or skin below the pinna. Varicella-zoster virus can be isolated from the vesicle, which establishes the diagnosis of herpes-zoster oticus or Ramsay Hunt syndrome. In this case, the varicella-zoster virus became latent in the geniculate ganglion during childhood chickenpox and reactivated many years later.

### Major Laboratory Findings

Remarkably few laboratory abnormalities exist in Bell's palsy. The patient has a normal hemogram,

erythrocyte sedimentation rate, and serum electrolytes. The CSF is normal. If the CSF has a pleocytosis, the facial palsy etiology is likely due to an inflammatory or infectious process, such as varicella-zoster virus, Lyme disease, neurosyphilis, or sarcoidosis. Cranial MRI with gadolinium may show enhancement of the facial nerve within the facial canal. The EMG, normal for the first 3 days, shows a steady decline in activity and after 10 days, denervation potentials begin to appear. At autopsy of individuals without a history of Bell's palsy, herpes simplex viral DNA can frequently be detected by polymerase chain reaction in the geniculate ganglia. This suggests that the virus may become latent in that ganglion, but whether exacerbation of the latent virus produces Bell's palsy remains controversial.

### Principles of Management and Prognosis

Management of the patient with Bell's palsy is divided into treating the acute facial palsy and preventing complications. If there is incomplete paralysis of facial muscles, there is an excellent prognosis for full to satisfactory recovery that spontaneously occurs within 2 months. Should the facial paralysis be complete, full to satisfactory recovery spontaneously occurs in about 80% of patients over 1 to 3 months. In an effort to improve outcome, patients are often given corticosteroids for several days, with the hypothesis that the corticosteroids will lessen facial nerve edema, reduce nerve pressure, and prevent nerve ischemia. If one believes herpes simplex virus may be the etiology, the antiviral drug acyclovir is given for a week. Observing vesicles on the ear pinna suggests another antiviral drug (famciclovir, penciclovir, or high-dose acyclovir) should be given to treat the varicella-zoster viral infection.

Frequently the patient will have facial weakness such that he or she cannot fully close the eyelid, exposing the cornea to abrasions and drying. After applying ointment, these patients should tape their eyelid closed while sleeping. Some patients have diminished tearing in the involved eye and require frequent application of liquid tears. A few patients will have aberrant regeneration of the facial nerve during recovery, leading to synkineses (unintentional facial movements accompanying volitional facial movements).

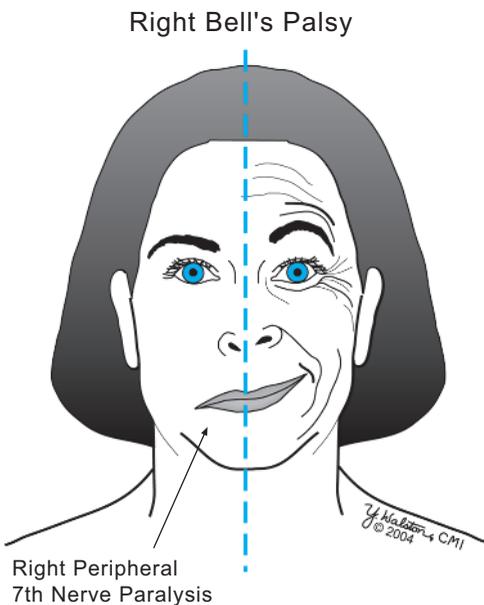


Figure 6-3 Bell's palsy.

## RECOMMENDED READING

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- British Medical Research Council. *Aids to the Examination of the Peripheral Nervous System*. 4th ed. Philadelphia: W. B. Saunders; 2000. (Superb booklet that outlines how to test each muscle, describes areas of sensation for all peripheral nerves, and easily can be kept in the physician's bag.)
- Green DA, Stevens MJ, Feldman EL. Diabetic neuropathy: scope of the syndrome. *Am J Med* 1999;107(suppl):2S–7S. (This journal supplement has a series of useful articles on diabetic neuropathy.)
- Hughes RAC. Peripheral neuropathy. *BMJ* 2002;324:466–469. (General review of causes and workup for all patients with peripheral neuropathy.)
- Katz JN, Simmons SP. Carpal tunnel syndrome. *N Engl J Med* 2002;346:1807–1812. (Excellent review.)
- Marenda SA, Olsson JE. The evaluation of facial paralysis. *Otolaryngol Clin N Amer* 1997;30:669–682. (Reviews causes of facial paralysis, including Bell's palsy, clinical findings, laboratory tests, and natural history.)
- Sweeney CJ, Gilden DH. Ramsay Hunt Syndrome. *J Neurol Neurosurg Psychiatry* 2001;71:149–154. (Reviews facial paralysis due to reactivation of varicella-zoster virus.)

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# 7 DISORDERS OF THE SPINAL CORD AND VERTEBRAL BODIES

## Overview

For many years, the spinal cord was conceived as a conduit that carried impulses from the brain to the trunk and limbs and vice versa. We now know that spinal cord functions are not solely passive, but rather modulate or generate many afferent and efferent pathways. For example, endorphin-containing neurons in the dorsal horn actively modulate afferent peripheral pain fiber impulses, resulting in diminishment or enhancement of perceived pain. Important aspects of normal walking appear to be generated from clusters of motor neurons located in the lower thoracic and upper lumbar spinal cord. Rapid limb withdrawal from a painful stimulus and deep tendon reflexes do not involve the cortex but result from local circuitry in the cord.

The spinal cord, which is about the diameter of a thumb, extends caudally from the medulla to the first or second lumbar vertebra in adults and slightly lower in infants (Figure 7-1). From L2 to S2 the central vertebral canal is composed of nerve roots, ending in the cauda equina. The absence of spinal cord below L2 is the reason why a lumbar puncture can be safely performed in the lower lumbar area.

Spinal cord dysfunction results from traumatic, ischemic, nutritional, malignant, or degenerative conditions. Diseases affecting the spinal cord usually cause three clinical pictures. Two involve spinal cord parenchyma and one involves spinal cord roots. The first is degenerative with loss of specific spinal cord elements, as seen in amyotrophic lateral sclerosis (ALS) and subacute combined degeneration (vitamin B12 deficiency). The second is from a lesion at one level of the spinal cord as seen in back or neck trauma, cervical myelopathy from a central protruding intervertebral disk, or acute transverse myelitis. The third is from compression of exiting spinal cord nerve roots, producing a radiculopathy (sensory and motor dysfunction of a single dermatome/myotome) due to focal lesions such as posterolateral prolapse of a vertebral disk or a neurofibroma compressing a spinal cord root.

Clinical signs depend on the level of the spinal cord damage and whether the damage involves part or all of the cord. Thus to understand the clinical signs produced by lesions in spinal cord parenchyma, one must know the differences between upper motor neuron and lower motor neuron dysfunction (Figure 7-2) and anatomic location and function of key spinal cord tracts (Figure 7-3 and Tables 1 and 2).

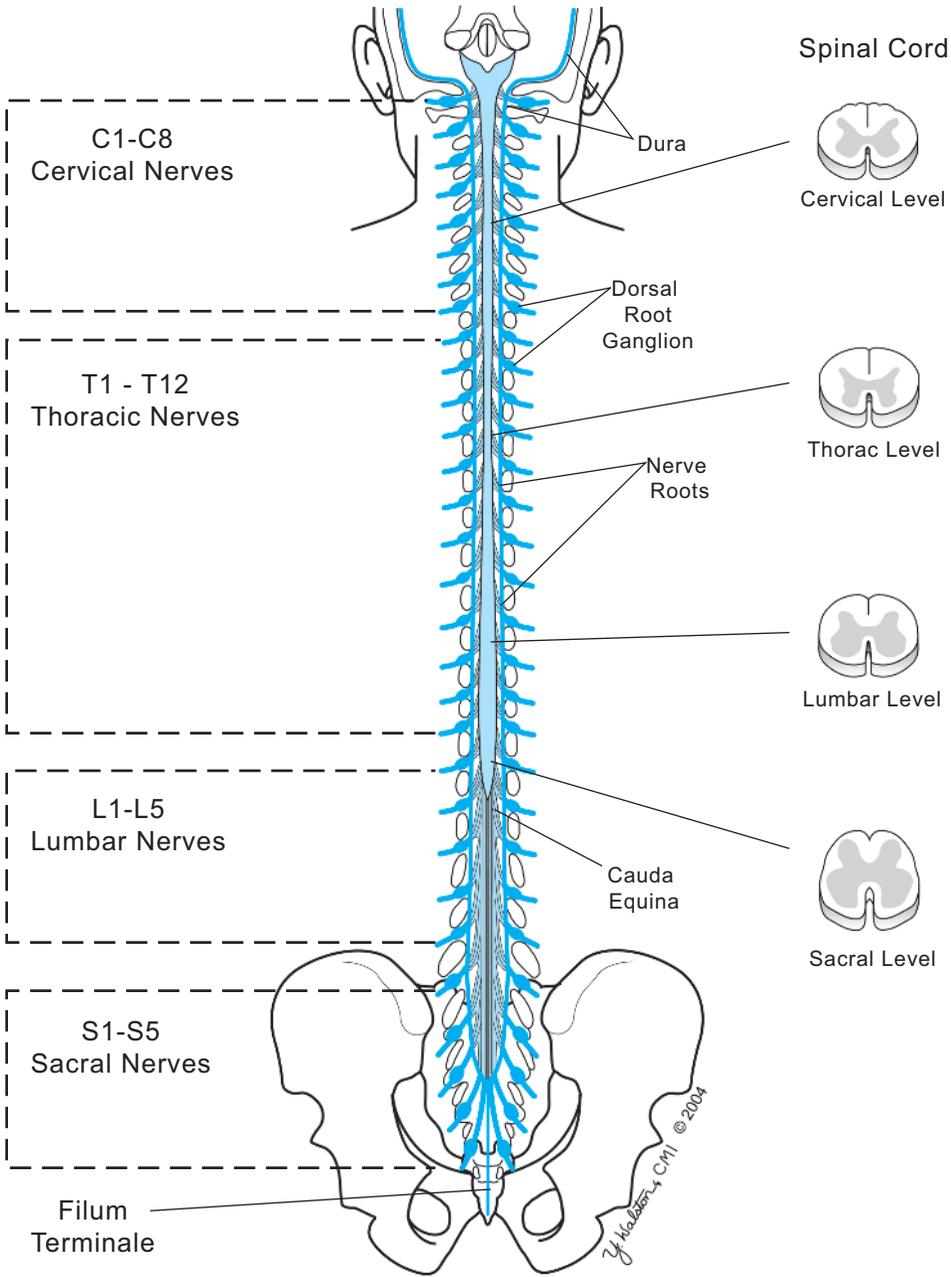


Figure 7-1 Diagram of spinal cord and vertebral bodies.

## Amyotrophic Lateral Sclerosis

### Introduction

ALS is a prototype system disease that exclusively affects upper and lower motor neurons. This progressive, fatal, degenerative disease of bulbar, spinal cord, and cortical motor neurons has no

known cause. The disease is commonly known as Lou Gehrig disease, named for the famous baseball player who developed ALS. The term “amyotrophic” refers to muscle atrophy and “lateral sclerosis” refers to hardening from gliosis following degeneration of the lateral corticospinal tracts, noted on palpation of the spinal cord.

Characteristic	Upper motor neuron	Lower motor neuron
Location	Up	Down
Muscle tone	Up	Down
Reflexes	Up	Down
Toes (Babinski)	Up	Down
Muscle bulk	No change	Down
Fasciculations	Absent	Present

**Figure 7-2** Characteristics of upper and lower motor neuron disease.

The incidence of ALS is 1/100,000, with a prevalence of 4/100,000. The peak age of onset ranges between 55 and 75 years of age. The male-to-female ratio is 1.5:1. Most cases are sporadic but 5% are hereditary.

In the typical case, the diagnosis is straightforward. For atypical-onset cases, the differential diagnosis includes cervical spondylotic myelodisculopathy, multifocal motor neuropathy, X-linked spinobulbar muscular atrophy (Kennedy's disease), thyrotoxicosis, and elongated spinal cord tumors.

### Pathophysiology

The cause of sporadic ALS is unknown, but several hypotheses exist. The first is excessive extracellular glutamate in the spinal cord resulting from a defect in glutamate reuptake. Excessive glutamate could stimulate calcium-permeable *N*-Methyl-D-aspartate (NMDA)-receptor channels, allowing excessive entry of extracellular calcium into motor neurons. Evidence for this hypothesis is that ALS patients have elevated levels of glutamate in the blood and CSF. In addition, riluzole, a glutamate antagonist, slightly improves survival in ALS.

Autoimmune hypotheses are based on observations that activated T lymphocytes and deposit of immunoglobulin are found in the spinal cord gray matter and motor cortex of patients. However, trials of several immunosuppressant drugs have not improved patient survival. Lack of critical neurotrophic factors for motor neurons has been suggested as the etiology, but specific motor neuron growth factors have yet to be identified. Abnormal free-radical formation with accumulation of superoxide in the spinal cord has been proposed based on the finding that 20% of hereditary ALS stems from a missense mutation in the Cu/Zn superoxide dismutase (SOD1) gene on chromosome 21. However, studies suggest that the mutated SOD1 protein acts through an unknown "gain of function" and not "loss of function," as knockout mice lacking this gene do not develop signs of ALS. Whatever the abnormal mechanism, the final common pathway appears to trigger apoptosis of motor neurons.

Motor neurons of the spinal cord and brainstem show simple atrophy and intracytoplasmic lipofuscin accumulation, leading to cell death and secondary astrocytic gliosis. There is significant reduction in the number of large motor neurons in the anterior horns of the cervical and lumbar spinal cord, with a corresponding loss of large myelinated axons in the ventral roots and peripheral nerves innervating the limbs. Interestingly, there is little anterior horn cell loss in the thoracic and sacral spinal cord, accounting for relative preservation of autonomic function and bladder and bowel function. The lower cranial nerves leading to facial muscles (especially CNs VII, IX, and X to XII) are more affected than cranial nerves supplying oculomotor muscles (CNs III, IV, and VI). In patients with prominent upper motor neuron signs, there is severe depletion of Betz cells and pyramidal neurons of the fifth layer of the motor cortex, with secondary degeneration of the corticospinal tracts.

Loss of lower motor neurons leads to muscle fiber denervation and weakness. Studies show that weakness progresses at a relatively constant rate throughout most of the disease. In early stages of the illness, a compensatory mechanism enables denervated muscles to become reinnervated and regain function. Following death of a motor neuron, a denervated muscle fiber produces an unknown trophic factor that signals adjacent motor

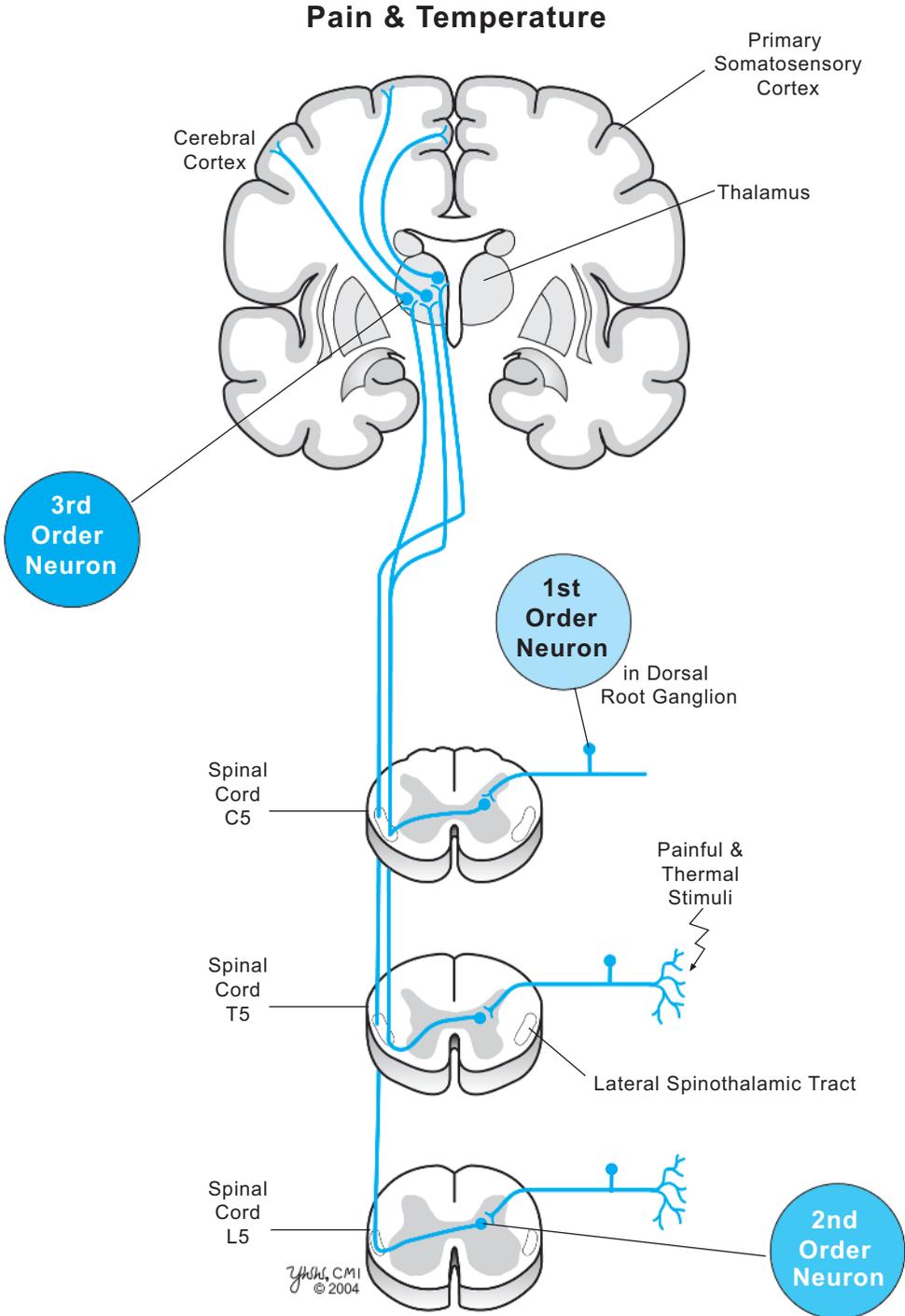


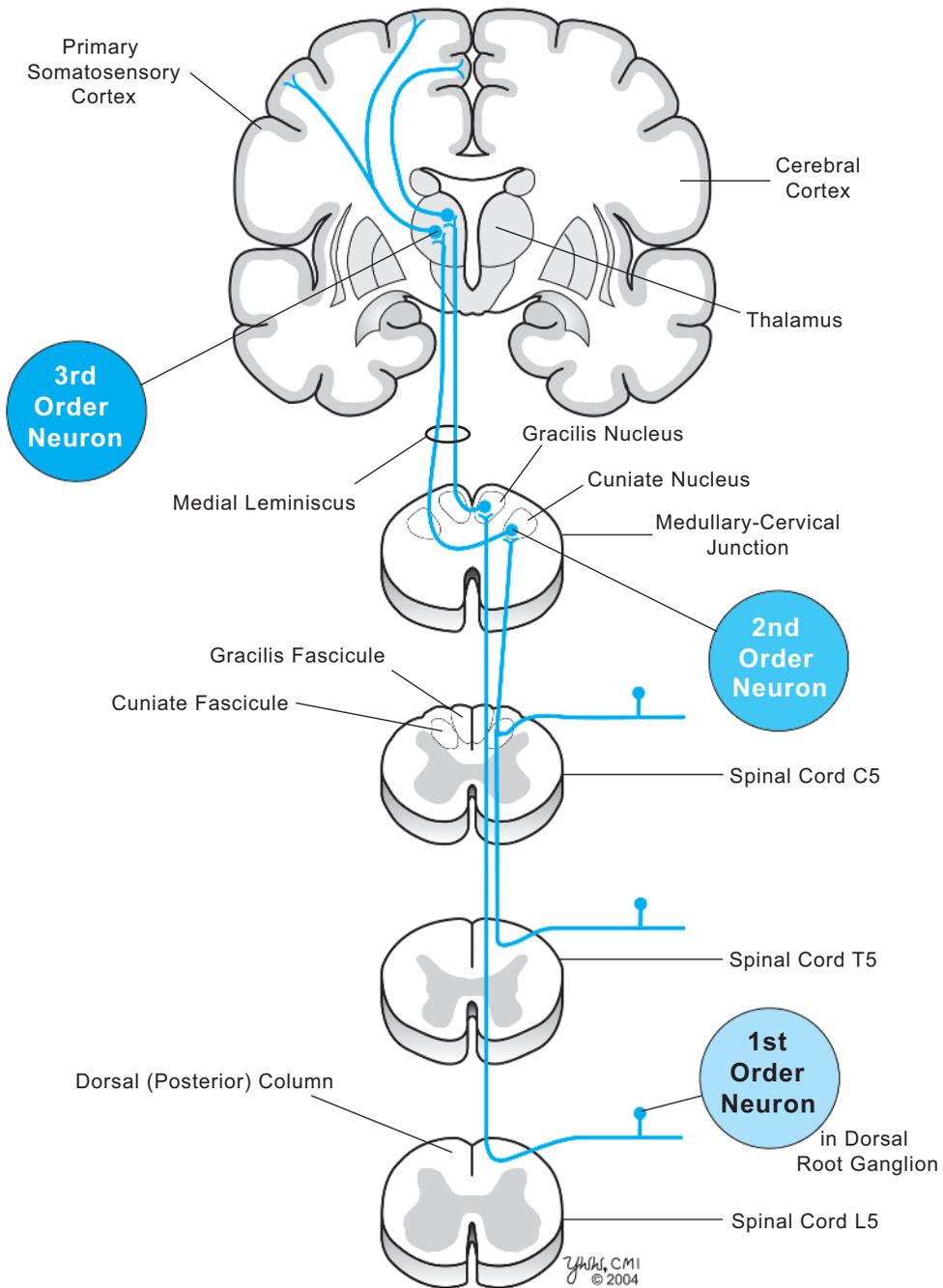
Figure 7-3 Diagram of cervical, thoracic, and lumbar cord, with pathways. (a) Pain and temperature. (Continues)

axons to send a branch axon (sprouting) toward the denervated fiber, with subsequent reinnervation of the fiber. This compensatory mechanism eventually fails when the replacement motor neuron dies.

### Major Clinical Features

Symptoms and signs of ALS are those of progressive upper and lower motor neuron loss. Loss of motor cortex neurons (upper motor neurons)

## Vibration & Position Sense



**Figure 7-3** (b) Vibration and position sense. (Continued)

leads to (1) limb spasticity, (2) hyperactive reflexes, (3) Babinski signs, (4) variable limb paresis, and (5) pseudobulbar palsy (dysarthria, dysphagia, and pseudobulbar affect with emotional reactions that are labile, exaggerated, and often inappropriate).

Loss of anterior horn neurons (lower motor neurons) causes (1) arm and leg muscle weakness that is symmetrical or slightly asymmetrical, (2) muscle atrophy, (3) widespread muscle fasciculations, (4) eventual loss of reflexes, and (5) respira-

**Table 7-1 Major Spinal Cord Tracts and Their Function**

Tract	Direction	Function	Location in Spinal Cord	Point of Tract Crossing to Opposite Side of Spinal Cord or Medulla
Corticospinal	From brain	Motor	Lateral	Medulla
Spinothalamic	To brain	Pain and temperature	Lateral	Near site of spinal cord entry
Dorsal column	To brain	Vibration and position sense	Posterior	Medulla

tory weakness from loss of phrenic nerve neurons to the diaphragm and neurons to accessory respiratory muscles.

Loss of bulbar lower motor neurons produces (1) atrophy of the tongue (small tongue with serrated edges), (2) fasciculations of tongue, (3) atrophy of masseter muscle and muscles involved in swallowing, producing dysphagia that can cause choking and malnutrition, (4) dysarthria, making speech slow and difficult to understand, and (5) mild-to-moderate lower facial muscle weakness and atrophy.

Of note, muscles involved in eye movements and bladder and bowel function are seldom involved. Sensation, autonomic nerve function, and cognition are preserved.

The weakness usually begins distally in the limbs and progresses to involve bulbar muscles, but in 20% of cases the process begins in bulbar muscles. Upper motor neuron signs may predominate early, but subside as the lower motor neuron disease progresses and masks them.

### Major Laboratory Findings

No specific diagnostic test for ALS exists. The hemogram, electrolytes, and liver and renal function studies are normal. Serum CK is mildly elevated, especially in rapidly progressive disease. CSF

is usually normal but may have a slightly elevated protein level.

The EMG shows evidence of widespread denervation involving muscles of multiple myotomes. Common findings include (1) fibrillations and positive sharp waves, (2) reduced motor unit firing rates, and (3) neurogenic motor units of long duration, multiple phases, and increased amplitude (large polyphasic motor unit potentials). Early motor nerve conduction velocity is normal, but slows later in the illness due to loss of the large myelinated axons that have the fastest conduction.

A muscle biopsy is occasionally done when the diagnosis is uncertain. Involved skeletal muscle fibers show changes typical for denervation, which include pyknotic nuclear clumps involving sarcolemmal nuclei and atrophy of fibers leading to small angulated fibers with concave borders that are all the same fiber type. Early on, the atrophic fibers are scattered, but later they occur in clusters called “group atrophy.” The cluster has all the same fiber-type staining. Normally, a cross section of skeletal muscle stained for fiber type presents a checkerboard appearance of types I and II fibers. Group atrophy is seen when muscle fibers lose their original motor unit, then gain a new motor unit from sprouting of an adjacent motor nerve

**Table 7-2 Major Spinal Cord Neuronal Groups**

Name	Function	Location in Spinal Cord
Anterior Horn	Lower motor neurons	Ventrolateral gray matter
Dorsal Horn	Modulation of afferent sensory impulses	Dorsolateral gray matter
Intermediolateral Horn	Sympathetic neurons	Intermediolateral gray matter of thoracic spinal cord
Lateral Horn	Parasympathetic neurons	Lateral gray matter of sacral spinal cord

that in turn dies, leaving a group of muscle fibers all of the same type.

## Principles of Management and Prognosis

No drug has been found that stops the progressive loss of motor neurons. However, riluzole increases survival of ALS patients by 3 to 6 months. The goal of management is to make the patient as functional and comfortable as long as possible. Family and friends are valuable in supporting the patient and minimizing the reactive depression that commonly develops. Usually a multidisciplinary team approach is taken for the medical care. As patients weaken, crutches and wheelchairs are needed. When dysarthria becomes severe, assistive communication devices allow patients to continue expressing themselves. Managing dysphagia presents a challenge. Patients can swallow semisolid foods (pureed or blenderized table foods) better than solid foods or liquids. To prevent malnutrition and cachexia, a feeding gastrostomy or jejunostomy may be required. Inability to swallow leads to pooling of saliva in the posterior pharynx, causing choking, drooling, and aspiration. Home suction equipment may be needed to minimize choking.

Respiratory weakness and failure become serious problems and usually trigger the terminal event of aspiration pneumonia. Early in the illness, a compassionate but frank interview with the patient and often family should focus on the patient's terminal wishes, and these should be placed in a living will. Some patients desire assisted ventilation terminally, while many others do not wish to undergo a tracheostomy and be mechanically ventilated for the rest of their life as they become progressively immobile. A vital capacity of less than 50% of that predicted increases the likelihood of development of respiratory failure.

For sporadic ALS, the mean illness duration is 2.5 years, but 10% to 15% of patients live 5 years or more. Younger patients live somewhat longer, as do patients presenting with limb weakness compared with those presenting with bulbar signs.

## Transverse Myelitis and Myelopathy

### Introduction

Myelitis implies inflammation within the spinal cord that may be focal or diffusely involve the

entire width of the spinal cord. Transverse myelitis implies involvement of a large portion of the cross-sectional area of the spinal cord, although such lesions often extend vertically in the spinal cord to varying extents. It is often clinically difficult to be certain that inflammation is actually at the lesion site and not from a myelopathic process such as ischemia. Therefore, the diagnosis of transverse myelitis is usually based on characteristic signs and symptoms plus neuroimaging that identifies a specific spinal cord level of involvement.

Acute transverse myelitis characteristically has signs and symptoms that progress rapidly and are monophasic. Causes of acute transverse myelitis and myelopathy include: (1) acute infections (viruses, bacteria, tuberculosis, and parasites), (2) postinfectious (following a nonspecific "viral" infection such as an upper respiratory infection), (3) autoimmune diseases (systemic lupus erythematosus and sarcoidosis), (4) complications of vaccinations (rabies vaccine derived from infected animal spinal cord and vaccinia), (5) spinal artery ischemia, and (6) multiple sclerosis.

Transverse myelitis is uncommon, with an incidence ranging from 1.5 to 4 cases 1 million people per year. Both children and adults are involved; there is no sex preference. Statistically, cases in children are commonly postinfectious, cases in young adults are often the first manifestation of multiple sclerosis or postinfectious, and cases in older adults are predominately a spinal cord mass, varicella-zoster virus infection, or ischemia.

### Pathophysiology

Damage to the spinal cord occurs by several mechanisms. One mechanism is from an expanding mass locally destroying that part of the spinal cord (such as a tuberculoma, ependymoma, bacterial abscess, or schistosoma in the spinal cord). The second mechanism is damage to the white matter from diseases that attack myelin (as seen in postinfectious transverse myelitis and multiple sclerosis). The third mechanism is local ischemic damage such as from angiitis in systemic lupus erythematosus and syphilitic tabes dorsalis or occlusion of spinal cord/radicular arteries from cardiac emboli or air emboli in decompression sickness. The fourth mechanism is direct infection of spinal cord oligodendrocytes or neurons, as seen in viral infections such as varicella-zoster virus following shingles or poliovirus.

Pathology in acute transverse myelitis demonstrates focal areas of segmental demyelination, with perivenous inflammation and variable amounts of necrosis.

### Major Clinical Features

Acute transverse myelitis is preceded by an upper respiratory infection in about 1/3 of patients. The illness is characterized by rapidly progressive (hours to a few days) signs that include (1) paraparesis or quadraparesis, (2) sphincteric disturbance, (3) bilateral Babinski signs, (4) variable back pain, and (5) sensory level most often at the thoracic level. If the sensory level is in the thoracic area, paraparesis develops while lesions involving the high cervical spinal cord often produce quadraparesis and impaired respiration. Lesions in the lumbar spinal cord produce varying degrees of leg weakness. Initially spinal shock may be present, with flaccid limb weakness and absent reflexes. Over weeks the spinal shock resolves and upper motor symptoms (leg spasticity, hyperactive reflexes, and Babinski signs) develop. The anatomic location of the lesion may not be lower than the identified sensory level. However, as afferent sensory fibers often climb several segments before synapsing with dorsal horn neurons, the lesion location may actually be several spinal cord segments higher. Headache and neck stiffness are uncommon unless the lesion is in the cervical spinal cord.

### Major Laboratory Findings

The CSF usually shows a pleocytosis (10–150 lymphocytes/mm<sup>3</sup>), moderately elevated protein level (80–500 mg/dL), and normal glucose level. CSF oligoclonal bands are unusual except when the lesion is due to multiple sclerosis. Infectious agents are rarely recovered from CSF but may be identified by PCR. In postinfectious transverse myelitis, no infectious agents are identified.

In postinfectious transverse myelitis, the T2-weighted MRI images usually demonstrate a spinal cord lesion that widens the spinal cord. The lesion, maximal in the central spinal cord area, often extends vertically over 1 to 3 spinal cord segments. Multiple sclerosis lesions extend over fewer segments than postinfectious lesions, may be present at several spinal cord sites, and often have similar

lesions in the white matter of the brain. Spinal cord tumors and abscesses are well circumscribed and strongly enhance with gadolinium.

### Principles of Management and Prognosis

Patients should be hospitalized, usually in an intensive care unit, during the acute stage. Catheterization of the bladder may be necessary. Corticosteroids are often given, but their efficacy is unproven. Physical therapy is required during rehabilitation. About 1/3 of patients make a good recovery, 1/3 a moderate recovery (able to walk) and 1/3 a poor recovery (need a wheelchair).

## Low Back Pain with Radiculopathy

### Introduction

One or more episodes of low back pain are experienced by 2/3 of adults. Although most do not seek medical attention, low back pain is a common reason patients see a physician. About 1% of U.S. adults are chronically disabled from low back pain and another 1% are temporarily disabled such that they seek worker's compensation. The estimated annual U.S. cost for back pain is \$40 billion. Low back pain affects men and women equally. The peak age of onset ranges between 30 and 50 years of age.

*Low back pain is a symptom and not a disease.* Studies have found that low back pain can develop from many spinal structures, including facet joints, ligaments, vertebral periosteum, paravertebral muscles, adjacent blood vessels, annulus fibrosus, and spinal nerve roots. In addition, back pain may be a referred symptom from abdominal structures such as the abdominal aorta, GI tract, kidney, bladder, uterus, ovaries, and pancreas. This chapter will focus primarily on low back pain from a laterally protruding lumbar disk that creates sufficient stenosis (narrowing) at the lumbar spine neural foramina to cause a radiculopathy (signs and symptoms belonging to one nerve root).

In the evaluation of a patient with low back pain, the clinician should first determine whether the back pain could be referred from the abdomen or is coming directly from a vertebral structure. A history of fever, recent weight loss, cancer, infection of the urinary or GI tract, drug abuse, human

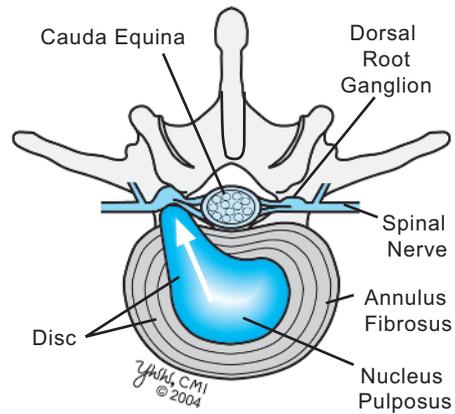
immunodeficiency virus (HIV) infection, or immunosuppression from drugs such as corticosteroids should prompt a careful physical exam with attention to the abdomen and the ordering of laboratory tests based on the history and exam. Attention should be paid to determine whether the low back pain is most likely infectious (e.g., epidural abscess), neoplastic (e.g., prostate cancer metastasis), arthritic (e.g., ankylosing spondylitis), or traumatic. Finally, the history and exam should determine whether a radiculopathy or cauda equina syndrome is present.

### Pathophysiology

The stability of the spine results from the integrity of four structures: vertebral bodies, intervertebral disks, ligaments between the vertebral bodies, and paraspinal and other muscles. The voluntary and reflex contractions of the paraspinal, gluteus maximus, hamstrings, and iliopsoas muscles are very important in preventing vertebral injury, as ligaments are not sufficiently strong to resist the enormous forces that affect the lower back. In the healthy disk, the center contains the gelatinous, spongy nucleus pulposus, which is surrounded by an envelope of fibrous tissue called the annulus fibrosus. These give the disk the ability to act as a shock absorber to the everyday trauma of walking and jumping. After the second decade, deposition of collagen, elastin, and altered glycosaminoglycans in the nucleus pulposus causes it to lose water progressively. The cartilaginous end plate becomes less vascular. The resulting disk becomes thinner and more fragile; it bulges, and with injury extrudes. Studies show disk bulging to be present in  $3/4$  of asymptomatic adults over the age of 50 years. However, the extrusion of the nucleus pulposus may produce local back pain from an inflammatory response and the extrusion fragment may compress or stretch nerve roots before they exit the neural foramina.

Since back pain also develops from other spinal structures, the cause of isolated low back pain is seldom determined, forcing the use of imprecise terms such as back strain or back sprain.

When the disk protrudes somewhat laterally, the protrusion may compress a nerve root (Figure 7-4). Lower extremity radiculopathy mainly comes from compression of L4, L5, and S1 nerve roots.



**Figure 7-4** Lateral protrusion of disc, top view. The disc compresses the nerve root as it exits the neural foramen.

Over 90% of clinically significant problems stem from an L4-to-L5 or L5-to-S1 disk herniation, with compression of the L5 or S1 nerve root. Upper-extremity radiculopathies develop mainly from compression of C5, C6, and C7 nerve roots.

### Major Clinical Features

Patients with back disease may complain of pain, stiffness, limitation of movement, and spine deformity. Four types of pain are described. Local pain comes from irritation of pain fibers in the lower back and is often described as a steady and aching pain that is not well circumscribed and occasionally becomes sharp. Patients usually complain of back pain worsened by bending, twisting, or lifting and may often use involuntary splinting or tightening of back muscles to prevent vertebral movement affecting the painful area. Referred pain may occur, with patients describing a diffuse and deep ache in the buttocks, pelvis, flank, lateral hip, groin, and anterior thigh. Muscle spasm pain is usually paraspinal in nature and associated with paraspinal muscles that prevent motion of the involved vertebrae. Radicular or “root” pain from stretching, irritation, or compression of a spinal root is described as sharp, intense pain (sciatica) that radiates from the back down a leg in varying patterns depending on the root involved (Figure 7-5). Coughing, sneezing, and straining at stool (Valsalva maneuvers) may aggravate the pain.

As noted above, the patient should not have an abdominal mass or bruit that would suggest

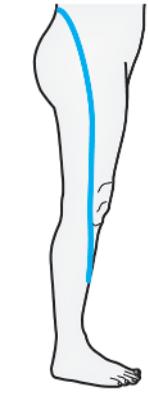
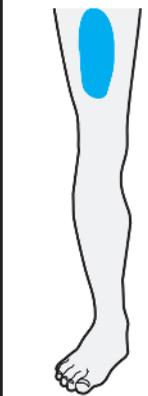
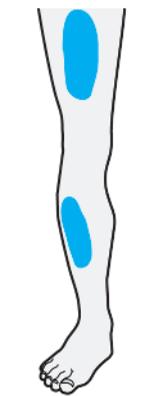
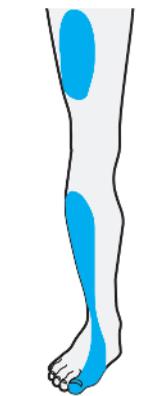
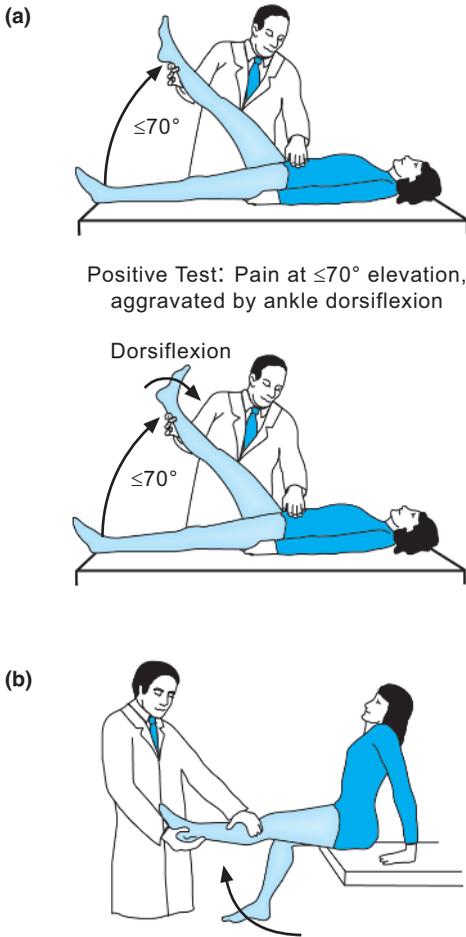
Nerve Root	L3	L4	L5	S1
Pain				
Numbness				
Weakness	Quadriceps	Quadriceps	Anterior Tibialis	Gastrocnemius
Lost Reflex	KJ	KJ	None	AJ

Figure 7-5 Lumbar radiculopathy. KJ, knee injury; AJ, ankle jerk.

referred abdominal pain to the back. An enlarged prostate should not be present that would suggest possible metastasis to vertebrae.

Examination of the back should include inspection of the lower back to determine if local muscle spasms are present and if the pain increases by body movements such as bending forward or backward. The vertebral bodies should be gently palpated and percussed to determine whether focal tenderness is present. The presence of localized pain to a specific tender vertebra should raise concerns of a possible localized process such as epidural abscess, vertebral metastasis, or vertebral fracture. Neuroimaging is indicated in these patients. With the onset of acute radicular pain, the patient may prefer lying supine with the legs flexed at the knees and hips.

The straight-leg-raising test can often help in determining the presence of radicular pain. The patient may be sitting or lying supine. The leg is elevated slowly to about 70° and then the foot is dorsiflexed (Figure 7-6). Patients with radicular pain describe sciatica pain that radiates below the knee and not merely in the back or hamstring and is particularly intense in the buttock just lateral and below the sacroiliac joint. A radiculopathy may also produce relative numbness in a particular dermatome, leg paresthesias, weakness of muscles in the involved myotomes, and loss of the ankle or knee reflex (Figure 7-5). In the patient with chronic radiculopathy, the involved muscles may be hypotonic and atrophic.



**Figure 7-6** (a) Straight-leg-raising test. (b) Sitting straight-leg test.

L5 radiculopathy is common and usually due to an L4-to-L5 disk protrusion. Patients complain of pain in the hip, posterolateral thigh, lateral calf, and dorsal surface of the foot and first or second toes. Paresthesias may be felt in the entire territory or distal portion. Numbness may occur over the lateral calf and medial aspect of the dorsum of the foot, including the first two toes. Weakness, if present, involves extensors of the big toe and foot with difficulty walking on heels. The ankle jerk may or may not be diminished.

The patient with an S1 radiculopathy typically complains of pain in the midgluteal region, posterior part of the thigh, posterior calf and heel, and lateral foot to the 4<sup>th</sup> and 5<sup>th</sup> toes. Paresthesias and sensory loss occur mainly in the lateral foot and

toes. There may be weakness of plantar flexion of the big toe and foot, making walking on the toes difficult. Occasional hamstring weakness is noted and the ankle jerk is diminished or lost.

### Major Laboratory Findings

The CSF is normal or has slightly elevated protein. The EMG in a patient with radiculopathy shows no changes for 3 weeks. After 3 weeks, the radiculopathy produces sufficient root compression to produce denervation changes in innervated muscles that include fibrillations and positive sharp waves. A MRI is the most sensitive neuroimaging technique used, but CT myelography can detect abnormalities as well. Epidural infections, tumors, and vertebral dislocations are easily detected. Herniated disks and whether the herniation impinges on a spinal root or neural foramina can be seen. It is important to note that disk abnormalities are commonly seen on neuroimaging, especially after middle age, and are often incidental and noncontributory to the patient's symptoms. Since anatomy is not function, neuroimaging must always be correlated with the history and neurologic exam.

### Principles of Management of Lumbar Disk Herniation and Prognosis

Back pain is usually divided into acute (<3 months duration) and chronic (>3 months). Patients with acute back pain have a high probability of natural improvement in both back pain, disability, and radicular signs. It has been estimated that less than 5% of patients will require surgical intervention, but many patients will progress to chronic back pain.

Patient care for both acute and chronic low back pain consists of (1) alleviating the back and leg pains, (2) activity changes, and (3) alteration in patient's lifestyle. For most patients, acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) will improve discomfort to tolerable levels. Tricyclic antidepressants may be helpful if the pain is distressing. Use of opioids may be required for brief periods if radicular pain is severe, but prolonged opioid usage is not beneficial. Muscle relaxants are similar to NSAIDs in benefit. Patients should be encouraged to return quickly to normal activities, but not strenuous activities requiring lifting and bending. Prolonged bed rest leads to

deconditioning and does not accelerate recovery. Spinal manipulation may offer temporary relief when administered, but should wait until one month after onset as spontaneous recovery often occurs by then. Traction, massage, diathermy, ultrasound, biofeedback, acupuncture, and transcutaneous electrical stimulation may offer temporary relief but have no proven long-term efficacy.

Lifestyle changes shown to be helpful in preventing recurrences as well as preventing chronic back pain include (1) weight reduction to ideal body weight, (2) cessation of smoking, (3) avoiding lifting heavy objects, and (4) regular aerobic exercise. Excess weight places awkward stresses on the back when lifting and twisting. The nicotine from smoking is thought to constrict vascular beds in the back, delaying natural recovery. Exercise programs strengthen paraspinal and abdominal muscles, helping to properly distribute loads on the spine when bending or twisting. Most exercise programs begin with walking short distances and simple back exercises, which slowly progress in duration and intensity. Regular exercises and swimming have been shown to increase range of motion, relieve back pain, and prevent recurrences.

Patients with fracture and instability, infection, tumor, severe motor weakness from nerve root impingement, or cauda equina syndrome (bladder or bowel dysfunction, “saddle” numbness in the perineum and medial thighs, and bilateral leg pain and weakness) often require immediate back surgery. Only 5% of patients with chronic low back pain will benefit from spinal surgery. Patients most likely to benefit are those with considerable neuro-

logic deficits related to a specific lumbar or sacral nerve root involvement that persists longer than 4 to 6 weeks and with neuroimaging that demonstrates a herniated disk. Patients with only back pain are the least likely to benefit from surgery. Injections of anesthetics or steroids in the lower back area (nerve blocks, facet injections, and epidural injections) are occasionally helpful for temporary pain relief, which may enable the individual to exercise.

## RECOMMENDED READING

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- Deyo RA, Weinstein JN. Low back pain. *N Engl J Med* 2001;344:363–370. (Good review of causes and conservative management of back pain.)
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## 8 DISORDERS OF THE BRAINSTEM AND CEREBELLUM

### Overview

The brainstem lies at the caudal end of the spinal cord and extend upward to the basal ganglia. No other part of the CNS is packed with so many critical axon tracts and nuclei. Important axon tracts include the corticospinal tract, conducting motor impulses from the cortex to the spinal cord, and long sensory tracts, conducting information from the spinal cord to the thalamus, cerebellum, and cortex. The nuclei for CNs II to XII lie in the brainstem. In addition, the brainstem contains the reticular formation, with centers that mediate sleep, arousal, and wakefulness, plus autonomic centers that control respiration, blood pressure, and GI functions.

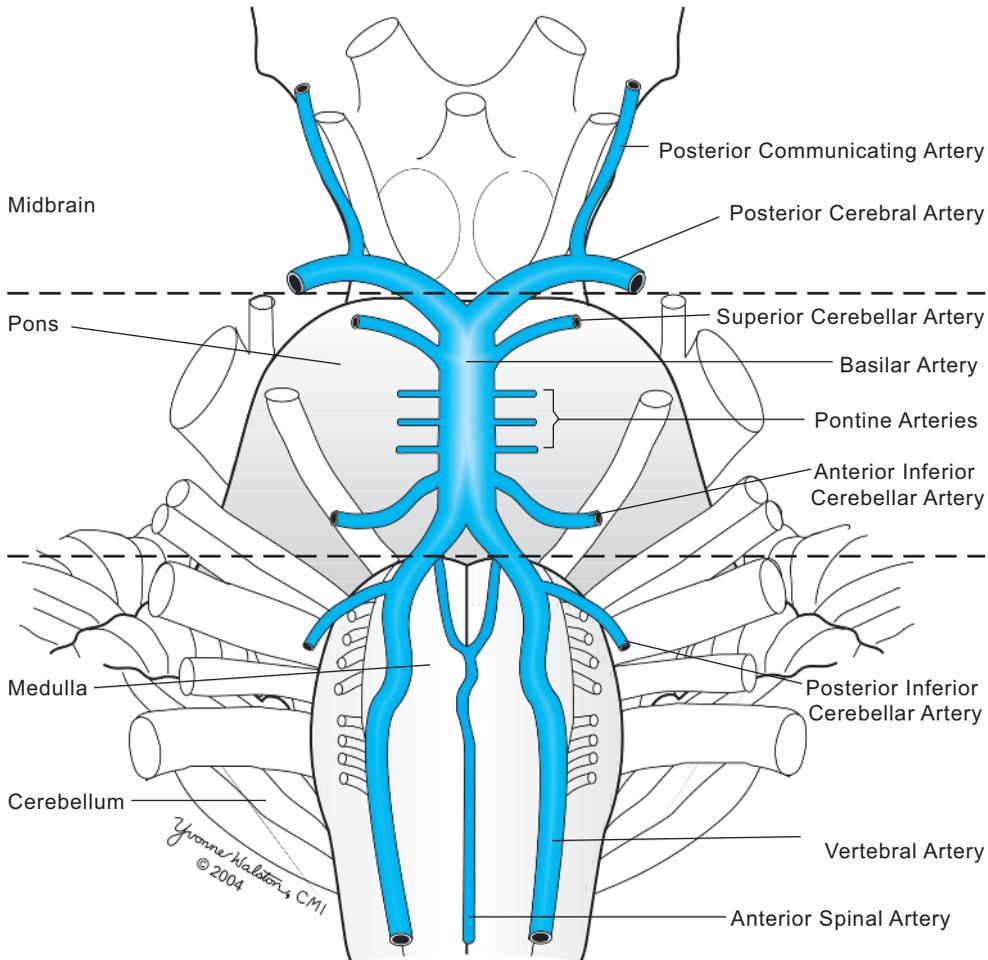
In determining the location of lesions involving the brainstem, it is useful first to determine whether the lesion is within the brainstem (intraaxial) or lies outside the brainstem along the cerebellopontine angle (extraaxial). Extraaxial lesions initially affect cranial nerves through entrapment or compression, with later signs developing from compressing brainstem structures or from compressing the aqueduct of Sylvius, producing obstructive hydrocephalus. A typical extraaxial lesion would be an untreated acoustic neuroma that begins in the Schwann cells of CN VIII, slowly extends medially out of the internal

auditory canal, and spreads along the cerebellopontine angle, trapping CN V and eventually compressing the pons.

In assessing the location of intraaxial brainstem lesions, it is useful to delineate structures along two planes: longitudinal and cross section. The longitudinal plane is usually divided into the mid-brain, pons, and medulla and the cross-sectional divisions are usually medial and lateral. Review of a neuroanatomy textbook is helpful in localizing important tracts and cranial nerve nuclei within this pattern of division.

Blood supply to the brainstem and cerebellum comes from both vertebral arteries and the basilar artery (Figure 8-1). There are many small penetrating arterioles that enter the brainstem from these major vessels. The arterioles generally supply one side of the medial brainstem (paramedian arteriole) or one lateral side (circumferential arteriole). Three arteries (superior cerebellar artery, anterior inferior cerebellar artery, and posterior inferior cerebellar artery) supply the cerebellum with blood and may have branches also going to the brainstem.

A variety of diseases affect the brainstem, but with a lower frequency than the same diseases affecting other brain regions. Brainstem tumors are most often astrocytic and slower growing than astrocytic tumors in the cortex. Bacterial abscesses



**Figure 8-1** Anatomy of vertebral and basilar arteries.

are rare, and most viruses causing encephalitis involve the brainstem less intensely. Hemorrhages involving the brainstem are uncommon. Ischemic strokes of the brainstem occur as lacunes or occlusions of penetrating brainstem arteries and are less common than cortical or basal ganglia strokes.

The cerebellum occupies about 10% of the brain volume but contains more neurons than the entire rest of the brain. The following is a brief review of cerebellar anatomy and function to help understand clinical abnormalities that develop from cerebellar diseases. The cerebellum is divided into the 3 functional divisions of the spinocerebellum, cerebrocerebellum, and flocculonodular lobe (Figure 8-2). Each division in the cerebellar cortex sends Purkinje cell axons to specific deep cerebellar nuclei and has different functions (Table 8-1).

Most input to the highly organized and redundant cerebellar cortex comes from many brainstem nuclei via excitatory mossy fibers that terminate on myriads of granule cells. These granule cell neurons then send inhibitory impulses to Purkinje cells. The inferior olive also sends excitatory input directly to Purkinje cells. Purkinje cells, the only output of the cerebellar cortex, send inhibitory impulses via a GABA neurotransmitter to neurons in the deep cerebellar nuclei that then send output to the brainstem and cerebral cortex.

Cerebellar neurons do not directly produce motor movements, but act more as a comparator that compensates for errors in movement by comparing intention with performance and making subtle adjustments. As such, patients with cerebellar diseases do not have weakness or sensory loss. Cere-

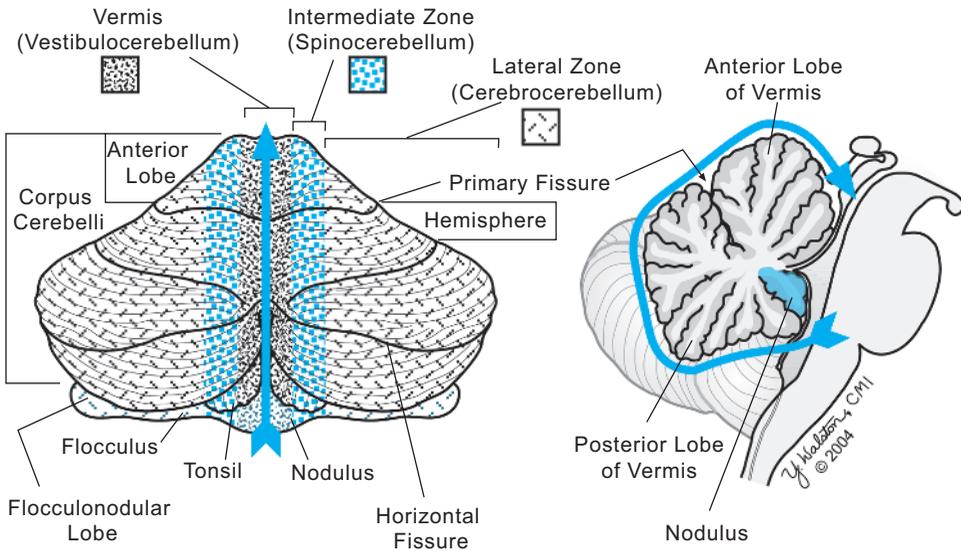


Figure 8-2 Anatomy of cerebellum.

bellar clinical problems are expressed as impaired coordination, imbalance, and even vertigo (Table 8-2). Dysfunction of midline cerebellar structures (vermis of spinocerebellum) produces imbalance problems of midline body structures such as gait and truncal ataxia, while cerebellar hemisphere dysfunction produces ataxia of limbs. Unlike the cerebral cortex, damage to one cerebellar hemisphere produces ipsilateral but not contralateral dysfunction.

A variety of diseases affect the cerebellum and include vascular events (ischemic and hemorrhagic strokes), tumors (medulloblastoma and childhood astrocytoma), toxins (alcohol and phenytoin), infections (chickenpox ataxia), and genetic disease (spinocerebellar ataxias and Freidreich's ataxia).

This chapter will focus on spinocerebellar ataxia due to a class of genetic diseases called triplet repeat nucleotide disorders; it expresses most of the clinical cerebellar problems. Chapter 19, "Neurologic Complications of Alcoholism," discusses alcoholic cerebellar degeneration.

## Lateral Medullary Infarction (Wallenberg Syndrome)

### Introduction

Lateral medullary infarction (LMI) is the classical stroke involving the lateral medulla (Figure 8-3)

Table 8-1 Cerebellar Functions by Location

Function	Cerebellar Origin	Deep Cerebellar Nucleus	Cerebellar Efferent Connections
Adjust Ongoing Movements of Axial and Proximal Limb Muscles	Spinocerebellum	Fastigial nucleus	Brainstem reticular formation, vestibular nuclei, and motor cortex
Adjust Ongoing Movements of Distal Limb Muscles	Intermediate spinocerebellum	Interposed deep nuclei	Red nucleus and motor cortex
Initiation, Planning, and Timing of Motor Movements	Cerebrocerebellum	Dentate nucleus	Red nucleus and premotor cortex
Axial Control and Vestibular Reflexes	Flocculonodular lobe	Direct connection to brainstem	Brainstem vestibular nuclei

**Table 8-2 Signs Suggestive of Cerebellar Dysfunction and Likely Cerebellar Localization**

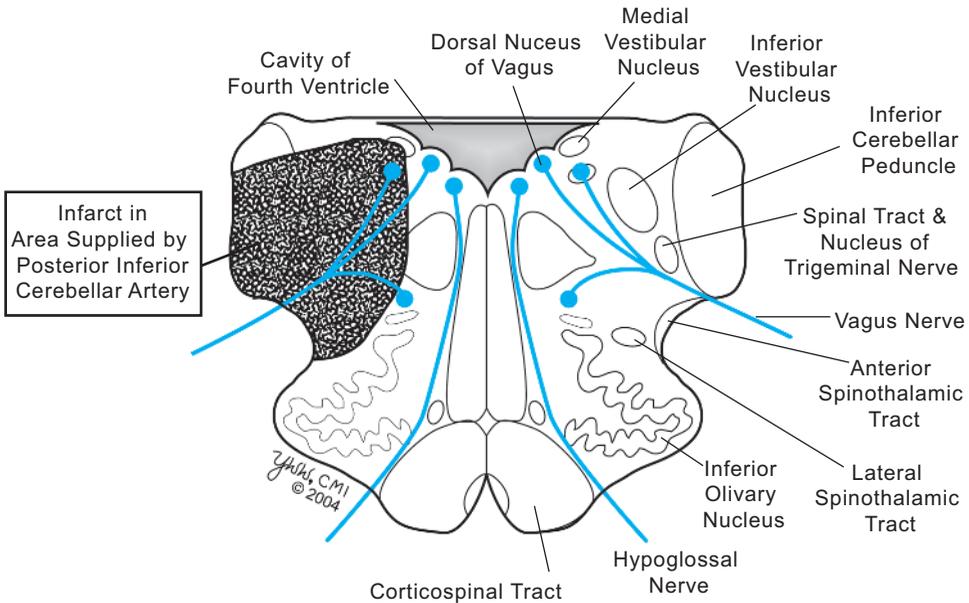
<b>Vermis (Midline Cerebellum)</b>
<ul style="list-style-type: none"> <li>• Gait ataxia Clumsy, uncertain, irregular, staggering steps in walking, with wide-based stance like “being drunk.” Tendency to fall to involved side.</li> </ul>
<ul style="list-style-type: none"> <li>• Truncal ataxia Inability to balance in sitting position at edge of table.</li> </ul>
<ul style="list-style-type: none"> <li>• Saccadic eye-movement abnormalities Conjugate eye movement rapidly to a target results in overshooting of eyes followed by overcorrections until target is reached.</li> </ul>
<b>Cerebellar Hemisphere</b>
Signs are ipsilateral to side of cerebellar lesion and more abnormal with fast limb movements than with slow movements.
<ul style="list-style-type: none"> <li>• Hypotonia Diminished arm and leg muscle tone give a loose feeling when passively moving the limb.</li> </ul>
<ul style="list-style-type: none"> <li>• Dysdiadochokinesis Irregular, uncoordinated rapid movements of hands or fingers. Often tested by asking patient to pat one palm alternately with the palm and dorsum of the opposite hand as rapidly as possible.</li> </ul>
<ul style="list-style-type: none"> <li>• Dysmetria Inaccuracies in judging distance and target when moving limb to a target with eyes closed.</li> </ul>
<ul style="list-style-type: none"> <li>• Cerebellar tremor Intention tremor develops when moving arm or leg that is perpendicular to the direction of the movement and often amplifies as the target is reached. Usually tested by asking patient to touch a target and then quickly touch the nose or to lift one heel and place it on the opposite knee and then move the heel down the shin.</li> </ul>
<ul style="list-style-type: none"> <li>• Ataxic dysarthria Poor coordination of articulation, resulting in slow, explosive speech.</li> </ul>
<b>Flocculonodular Lobe</b>
<ul style="list-style-type: none"> <li>• Nystagmus</li> </ul>
<ul style="list-style-type: none"> <li>• Transient vertigo Triggered by head or body movements from abnormal vestibuloocular reflex (reflex maintains eyes steady in space while head moves).</li> </ul>
<ul style="list-style-type: none"> <li>• Postural and gait dysfunction</li> </ul>
<ul style="list-style-type: none"> <li>• Vertigo, nausea, and vomiting Seen only in acute lesions.</li> </ul>

and dramatically demonstrates the multiple clinical signs that develop when there is damage to many important tracts and nuclei.

### Pathophysiology

The medulla receives its arterial blood supply from the vertebral artery via small branches that have considerable variability. The posterior inferior

cerebellar artery (PICA) is a large named artery that supplies blood both to the lateral medulla and to the posterior inferior aspect of the cerebellum. An LMI can result from stenosis, thrombosis, embolus, or dissection in the vertebral artery, or occlusion of the PICA or other small, unnamed, medullary arteries. Major risk factors include hypertension, diabetes mellitus, neck trauma, and atrial fibrillation.



**Figure 8-3** Lateral medullary infarction.

### Major Clinical Features

Of these patients, 3/4 develop acute onset of symptoms and 1/4 have symptoms that progress over hours to a day. The symptoms will vary depending on how medial the infarction extends and whether the caudal or distal medulla is maximally affected. More than 1/2 of patients experience multiple signs and symptoms. Dizziness, vertigo, nausea, vomiting, nystagmus, skewed vision (diplopia with targets diagonal to each other and not improved in any field of gaze), gait ataxia, and ipsilateral limb ataxia are prominent and are due to involvement of vestibular nuclei, inferior cerebellar peduncle, and/or vestibular nuclei–flocculonodular connections. Patients commonly complain of numbness and shooting pains on the ipsilateral side of the face and loss of pain and temperature sensation on the contralateral side of the body caused by damage to the descending trigeminal nerve and spinothalamic tracts. Dysphagia and dysarthria from paralysis of the ipsilateral palate, pharynx, and larynx muscles are due to damage to the nucleus ambiguus of CN X. Horner's syndrome, with ipsilateral ptosis, miosis (small reactive pupil), and loss of facial sweating occurs from damage to ascending sympathetic tracts. Marked limb weakness is uncom-

mon and implies ventral medullary corticospinal tract involvement from a large medullary infarction or hemorrhage.

### Major Laboratory Findings

An MRI, which is more sensitive than CT, demonstrates ischemic infarction in the lateral aspect of the dorsal medulla. Magnetic resonance angiography (MRA) and vertebral arteriography may demonstrate stenosis or absence of blood flow in the PICA, vertebral, or basilar artery.

### Principles of Management and Prognosis

Patients require hospitalization with attention to their inability to swallow (50% will require an enterofeeding tube for several weeks). If marked vertigo, nausea, and vomiting are present, vestibular sedative drugs may transiently be required. Dysphagia, dysarthria, and vertigo usually improve over several weeks. Rehabilitation is needed to improve balance, coordination, and gait. Most patients will regain the ability to walk and function independently. To prevent subsequent strokes, patients benefit from controlling their vascular risk factors and using antiplatelet therapy.

## Spinocerebellar Ataxia (SCA 1)

### Introduction

Spinocerebellar ataxias (SCAs) are a group of genetic diseases characterized by progressive loss of coordination and balance. The incidence of SCA 1 is 1 to 2 cases per 100,000 population. In recent years, enormous gains have been made in understanding this heterogeneous group of diseases; over 17 different genetic diseases have now been characterized and are called SCA 1 to SCA 17. Most SCAs are autosomal–dominantly inherited. Three pathologic mechanisms of SCA have been identified. The most common type (over 60% of cases) is a polyglutamine disorder resulting from proteins with toxic stretches of polyglutamine. Other types are gene-expression disorders resulting from repeat expansions outside of coding regions or channelopathies resulting from disruption of calcium or potassium channel function (see Chapter 4, “Disorders of Muscle”).

Common features of many polyglutamine SCA diseases include: (1) onset in adulthood, (2) slow progression, (3) neuronal loss in the cerebellum, brainstem, and spinal cord, (4) instability and expansion of a trinucleotide repeat tract, (5) mutant protein aggregation or clumping in the nucleus of involved neurons, and (6) occurrence of anticipation or the tendency for disease onset to be more severe and occur at a younger age in the next generation. Trinucleotide repeat genetic diseases are recognized to cause a wide variety of diseases that involve the basal ganglia (Huntington’s disease), muscle (myotonic muscular dystrophy), mental retardation (fragile X syndrome), motor neuron loss (spinobulbar muscular atrophy), and ataxia (Freidreich’s ataxia, and SCAs). The expansion of the trinucleotide repeat part of the mutant gene may occur in noncoding regions (fragile X syndrome, Freidreich’s ataxia, and myotonic muscular dystrophy) or in coding regions (SCA and Huntington’s disease) where the protein contains an expanded repeated amino acid.

### Pathophysiology

SCA 1 results from mutation of the *SCA1* gene in chromosome 6p consisting of a highly polymorphic, unstable repeat expansion of DNA nucleotide bases cytosine, adenine, and guanine

(CAG). The nucleotide CAG encodes the amino acid glutamine. The *SCA1* gene codes for a novel 87-kd protein called ataxin-1. In normal *SCA1* genes, CAG may be repeated 6 to 44 times, producing an ataxin-1 protein that has 6 to 44 repeated glutamine amino acids that are stabilized by histidine repeats. However, in SCA 1 disease, the mutant gene develops an expansion of CAG repeats from 39 to over 80 uninterrupted repeats and the mutant ataxin-1 protein has 40 to 81 repeat glutamine amino acids. The length of the trinucleotide repeat increases in the next generation due to gene instability, especially if the father transmits the disease. The longer the repeat length, the more severe and earlier the disease (anticipation). The function of ataxin-1 protein is unknown. The normal protein, found in all tissues, is located in the nucleus and cytoplasm of Purkinje cells and other brainstem and spinal cord neurons at 2 to 4 times the usual concentration.

Mutant proteins may cause disease by loss of function (loss of the mutant protein’s ability to conduct some critical function), gain of function (acquisition of abnormal function by the mutant protein), or abnormal aggregation and sequestering of other critical proteins. For the mutant ataxin-1 protein, evidence suggests the neuronal pathology is due to a gain of function or abnormal aggregation. Genetic mice lacking the mouse homologue of *SCA1* genes do not develop ataxia. Genetic mice that carry the normal human gene and express ataxin-1 protein remain entirely normal throughout life. However, genetic mice carrying a mutant gene expressing mutant ataxin-1 develop gait, coordination, and balance problems and have CNS pathology similar to the human disease.

Neuropathologic changes in SCAs 1 to 3 are fairly similar. Gross examination reveals atrophy of the cerebellum and pons, loss of the bulge of the inferior olive, and mild-to-moderate widening of sulci in the frontotemporal cortex region. Microscopically, there is severe loss of (1) Purkinje cells, maximally in the vermis, (2) dentate neurons, and (3) neurons in the inferior olive, pontine nuclei, and nuclei basis pontis. There is moderate loss of neurons in the anterior horns, cranial nuclei III, X, and XII, and cholinergic system of the forebrain. Mild neuronal loss occurs in the cerebral cortex. Extensive atrophy of the superior, middle, and inferior cerebellar peduncles, spinal cord posterior columns and spinocerebellar tracts, and corti-

ospinal tract is present. Neurons in the brainstem, but not the cerebellum, have one intranuclear inclusion containing ataxin-1 protein plus ubiquitin, a small molecule that attaches to abnormal proteins headed for degradation by a proteasome into reusable amino acids. Secondary gliosis develops in the cerebellar molecular layer, brainstem, and cerebral cortex.

### Major Clinical Features

The key clinical features are progressive gait ataxia, incoordination, dysarthria, and eventual bulbar dysfunction. In the third or fourth decade, patients begin to develop a slowly progressive gait ataxia, dysarthria, hypermetric saccades, nystagmus on lateral gaze, and deterioration of handwriting. With disease progression, spasticity develops, with hyperreflexia and Babinski signs, ataxia worsens, saccadic eye movements deteriorate, bradykinesia emerges, and dysmetria appears. In the late stage of the disease, muscle atrophy, hypoactive deep tendon reflexes, loss of position sense, and variable degrees of oculomotor paralysis develop. There is atrophy of the tongue, with severe dysphagia and dysarthria. Neuropsychiatric dysfunction and loss of complex executive functioning are common, but dementia is rare. Dystonia or chorea occasionally is seen. Disease progression lasts 10 to 15 years, with death resulting from aspiration and respiratory complications. Currently, the polyglutamine SCAs (SCAs 1 to 3, 7, and 17) are clinically indistinguishable.

### Major Laboratory Findings

The diagnosis of SCA 1 is based on DNA testing to detect an abnormal CAG trinucleotide repeat expansion of the *SCA1* gene on chromosome

6p23. Affected individuals have alleles with 39 to 81 CAG trinucleotide repeats. The genetic test is 100% sensitive and specific and available in many clinical laboratories.

### Principles of Management and Prognosis

To date, no therapy is successful in delaying or halting disease progression. Therefore, management is supportive. Canes and walkers help prevent patients from falling, and grab bars, raised toilet seats, and ramps aid in safer ambulation. Wheelchairs are necessary when the gait ataxia and imbalance become severe. Speech therapy and computer-based communication devices help patients with marked dysarthria. Weight control is important because obesity worsens balance and ambulation. Genetic counseling is helpful regarding decisions to have children, particularly since anticipation may occur in the offspring. Prenatal genetic testing is possible, but should be carefully weighed, as this is a late-onset disease.

### RECOMMENDED READING

- Kandel ER, Schwartz JH, Jessell JM. *Principles of Neural Science*. 4th ed. New York: McGraw-Hill; 2000 (Good review of brainstem and cerebellar anatomy and physiology.)
- Kim JS. Pure lateral medullary infarction: clinical-radiological correlation of 130 acute, consecutive patients. *Brain* 2003;126:1864–1872. (Discusses clinical features and correlations with MRI findings.)
- Margolis RL. The spinocerebellar ataxias: order emerges from chaos. *Curr Neurol Neurosci Rep* 2002;2:447–456. (Excellent review of clinical, pathologic, and genetic features of major SCAs.)

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# 9 DISORDERS OF THE CEREBROVASCULAR SYSTEM

## Overview

Stroke is a general term that implies damage to cerebral tissue from abnormalities of the blood supply. In simple terms, there may be insufficient blood to the brain (ischemic stroke or infarction), abnormal excess blood (hemorrhagic stroke or cerebral hemorrhage), or inadequate venous drainage of cerebral blood (venous stroke). Ischemic strokes represent 85% of all strokes, hemorrhagic strokes 14%, and venous strokes 1% (Table 9-1).

Stroke is the third-leading cause of death in the United States. Each year 500,000 people in this country develop a stroke and 150,000 die. Fortunately, since 1960 the incidence of strokes in the United States has significantly fallen, primarily due to better control of hypertension and diabetes mellitus, but there are still 4 million adults with stroke, with an overall prevalence of 750/100,000.

## Ischemic Strokes (Embolic and Lacunar)

### Introduction

Ischemic stroke occurs from lack of sufficient arterial blood flow in the territory of a specific cerebral

Table 9-1 Major Stroke Types\*

Stroke Type	Percentage (% of Each Category)
<b>Ischemic</b>	85%
• Carotid artery circulation	(55%)
• Vertebral/basilar artery circulation	(12%)
• Lacune	(31%)
• Other (vasculopathy, coagulopathy, sickle cell, hyperviscosity, and vasculitis)	(2%)
<b>Hemorrhagic</b>	14%
• Hypertensive hemorrhage	(50%)
• Amyloid angiopathy hemorrhage	(15%)
• Saccular aneurysm	(30%)
• Arteriovenous malformation	(3%)
• Other (infective aneurysm, cocaine, and anticoagulants)	(2%)
<b>Venous</b>	1%
• Thrombosis of cortical veins, deep cerebral veins, or dural sinuses	

\* Excludes stroke due to head trauma and subdural hematomas (see Chapter 18 on traumatic brain injury and subdural hematoma)

artery to maintain neuronal viability. The stroke can be due to (1) intrinsic vascular occlusion (thrombus) that occurs in the neck portion of the internal carotid artery, vertebral artery, or a cerebral artery or (2) vascular occlusion with material originating elsewhere (embolism) such as a stenotic site of the internal carotid artery or vertebral artery or from the heart. The large majority of emboli are blood clots, but occasionally they can be air, fat, or tissue fragments. Of the total number of ischemic strokes, 80% involve the carotid artery territory or anterior circulation and 20% involve the vertebrobasilar artery or posterior circulation.

Table 9-2 lists the major modifiable and unmodifiable risk factors for stroke.

**Pathophysiology**

Cerebral ischemia occurs from inadequate cerebral blood flow to a brain area. Total lack of oxygen and glucose to all brain neurons, as in a 12-to-15 second cardiac arrest, suppresses electrical activity and causes loss of consciousness. Normally cerebral arterial blood flow is 50 mL/100 g of brain per minute. When cerebral blood flow falls below 18 mL/100 g of brain per minute, cerebral function falters but neurons may remain alive. Thus, electrical activity ceases and sodium/potassium pumps begin to fail, but the neurons are viable and can recover function if blood flow improves. In a stroke, this area of potential recovery is called an *ischemic penumbra*. Blood flow below 8 mL/100 g of brain per minute results in neuronal death as early as 15 minutes after flow disruption. Neurons in the hippocampus and cerebellum are the most sensitive to ischemia, while neurons in the brainstem and spinal cord are the most resistant. Brain ischemia results in impaired energy metabolism, with accumulation of calcium ions in the intracellular space, elevated lactate levels, acidosis, and production of free radicals. Cellular homeostasis is disrupted, leading to neuronal death.

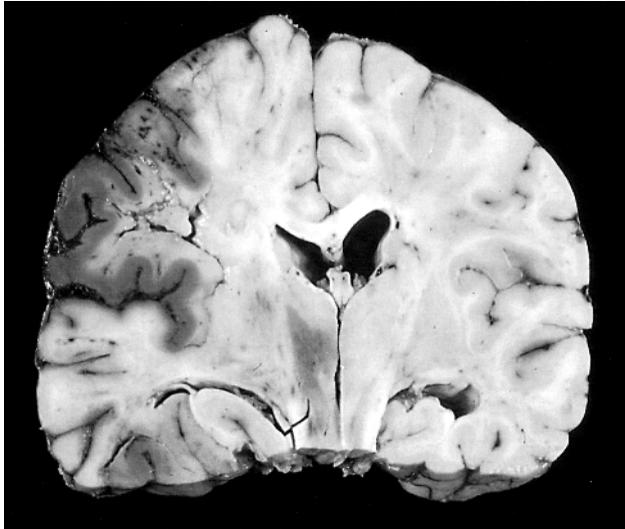
Stroke from occlusion of a specific cerebral artery causes a wedge-shaped infarction (Figure 9-1). If a large artery occludes, such as the middle cerebral artery, the stroke may involve that entire vascular territory, or portions may be spared depending on the degree of collateral circulation. With global hypotension, anoxia, or hypoglycemia, the stroke maximally involves the watershed territory between the middle and posterior

**Table 9-2 Risk Factors for Stroke**

<b>Risk Factor</b>	<b>Increase in Risk Over Normal Age-Matched Population</b>
<b>Modifiable</b>	
Hypertension	300%–600%
Diabetes mellitus	200%–400%
Smoking	150%–300%
Cocaine/crack	200%–500%
Atrial fibrillation	
Untreated	300%–500%
On warfarin	50%
Other heart abnormalities (mural thrombus, cardiomyopathy, acute myocardial infarction, mechanical heart valve, and infective endocarditis)	200%–600%
Obesity	200%
Serum lipid abnormalities	50%
Asymptomatic carotid artery stenosis	(Five-year increase)
60%–74% stenosis	10%
75%–94% stenosis	14%
>95% stenosis	10%
Total occlusion	5%
<b>Unmodifiable</b>	
Advancing age	Relative rates double every decade after age 55 years
Male gender	25%
Prior transient ischemic attack	400%
Heredity (first degree relative with stroke)	100%–400% depending on cause

cerebral arteries (parietal lobe) and between the middle and anterior cerebral arteries (anterior frontal lobe). If there is rapid reperfusion of the ischemic territory from lysis of the embolic clot, blood may leak from damaged small arterioles, capillaries, and venules, producing hemorrhagic transformation of the ischemic stroke.

Lacunar strokes are small strokes rarely greater in size than 10 mm in diameter and are highly associated with chronic hypertension. The lesions are caused by arteriole microvascular occlusions



**Figure 9-1** Ischemic infarction; wedge-shaped pathologic specimen. (Courtesy of Mark Becher, MD)

due to arteriosclerotic or lipohyalinosis changes of deep perforating arteries less than 200  $\mu\text{m}$  in diameter. The occluded vessel wall is disorganized, and replaced by connective tissue and occasionally macrophages. Lacunes are primarily located in the basal ganglia, brainstem, and occasionally centrum semiovale. The rate of developing subsequent lacunes is 5% per year, which is more than twice that for large-territory strokes.

Microscopically, a large vessel ischemic stroke shows little visible changes until about 6 hours later, when swelling of neurons, astrocytes, and endothelial cells begins. Neurons first swell, then shrink, develop chromatolysis (nuclei become eccentric, with hyperchromasia), and then die. Neutrophils are abundant after the first day. By day 2, microglia proliferate and become macrophages, engulfing myelin-breakdown products. Astrocytes proliferate, become reactive, and lay down glial fibers to produce gliosis. Neovascularity slowly develops and renourishes the damaged brain. Gradually over months the infarcted brain products are reabsorbed, producing a glial-lined cavity of variable size.

The mechanism of natural stroke recovery is incompletely understood. Possible mechanisms for motor recovery include (1) recovery of motor neuronal excitability as blood flow increases, (2) activation of partially spared corticospinal tract pathways, (3) alternate behavioral strategies to use limbs, (4) parallel motor pathway activation via noncorti-

spinal tracts or the ipsilateral corticospinal tract, (5) movement of the functional motor cortex within the existing domain, and (6) neuroplasticity of the motor cortex to a new brain area. There is increasing evidence that the motor cortex is not fixed, but plastic and can expand or shrink within the existing site based on clinical demand and can even move motor function to remote sites.

### Major Clinical Features

Onset is sudden or the patient awakens from sleep with the completed stroke, but only rarely do stroke signs progress over 1 to 2 days. Table 9-3 lists the common clinical features of lacunar, anterior circulation, and posterior circulation strokes while Figures 9-2a and 9-2b show the location and distribution of the major arteries. Two-thirds of lacunes are asymptomatic, while most cortical strokes are symptomatic. Overall, the hemiparesis is severe in 60% of cases, moderate in 20%, and mild in 20%. Broca's aphasia is more common than Wernicke's aphasia, but severe left middle cerebral artery strokes will have global aphasia (see Chapter 11, "Disorders of Higher Cognitive Function").

### Major Laboratory Findings

Tests are performed to diagnose a stroke, identify its location, and determine the cause and source. Com-

**Table 9-3 Clinical Features of Common Strokes**

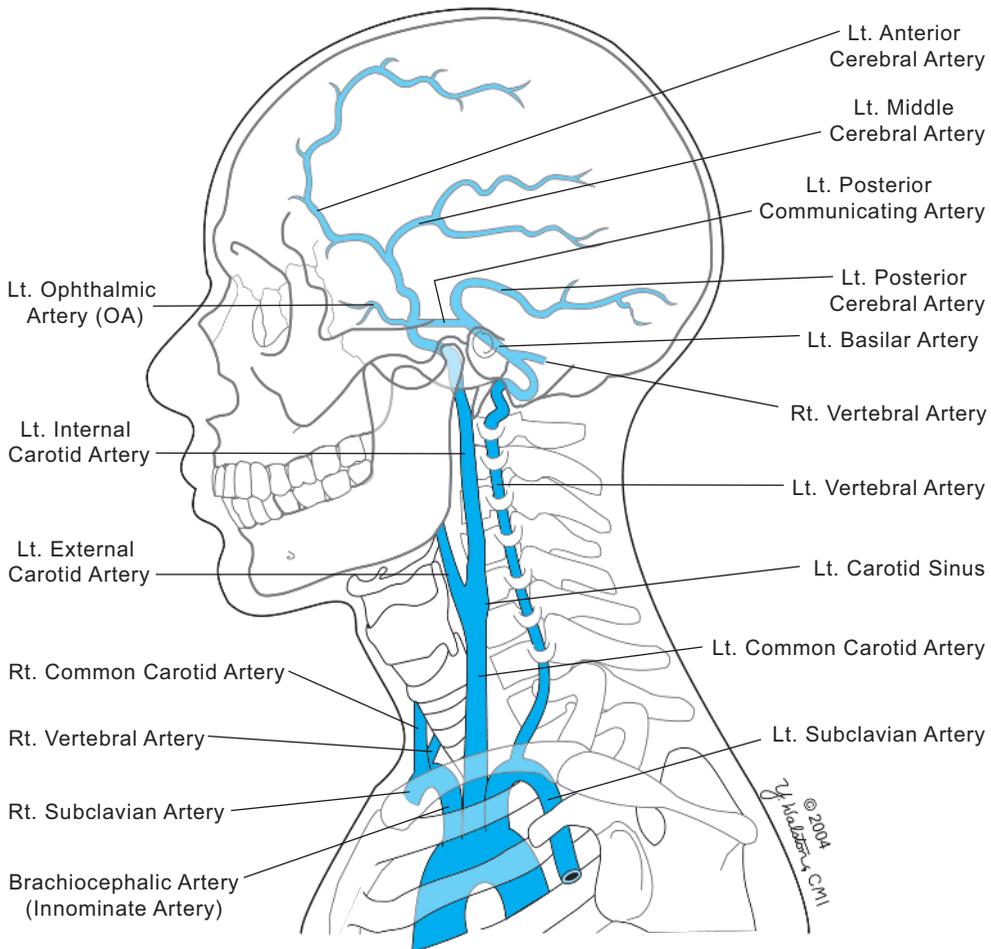
Arterial Territory of Stroke	Clinical Presentation*
Left Middle Cerebral Artery (Mid-Frontal and Parietal Lobes)	Aphasia, contralateral hemiparesis, contralateral hemisensory loss, homonymous hemianopia, and dysphagia
Right Middle Cerebral Artery (Mid-frontal and Parietal Lobes)	Contralateral hemiparesis, contralateral hemisensory loss, homonymous hemianopia, dysphagia, and apraxia
Anterior Cerebral Artery (Frontal Pole and Medial Aspect of Frontal and Parietal Lobes)	Contralateral leg weakness and sensory loss
Vertebral/Basilar Artery	
Wallenberg Syndrome from Posterior Inferior Cerebellar Artery (Medulla and Cerebellum)	Vertigo, nystagmus, dysphagia, and dysarthria with ipsilateral Horner’s sign (miosis, ptosis, and diminished sweating on face), diminished facial pain and temperature perception, limb ataxia, and contralateral loss of trunk and limb pain and temperature
Mid Basilar Artery (Pons and Cerebellum)	Often involves bilateral branches, producing signs that include facial weakness, quadraparesis, dysarthria, dysphagia, vertical and horizontal nystagmus, ptosis, skew deviation of vision, limb ataxia, and diminished level of consciousness. Locked-in syndrome occasionally develops, with complete loss of voluntary limb and face movement, retained consciousness, and voluntary vertical eye movements.
Top of Basilar Artery (Midbrain, Occipital Lobes, and Temporal Lobes)	Involves midbrain and posterior cerebral arteries, producing disruption of voluntary vertical gaze, CN III palsies, ataxia, somnolence, homonymous hemianopia or quadrantopia, and occasionally loss of recent memory
<i>Lacunar stroke territory</i>	
Internal Capsule	Contralateral hemiparesis and hemisensory loss without aphasia or visual loss
Upper-Half Brainstem/Cerebellum	Combinations of ataxia, vertigo, diplopia, dysarthria, Horner’s sign, contralateral sensory loss, ipsilateral facial weakness, and ipsilateral facial sensory loss
Lower-Half Brainstem	Contralateral hemiparesis without sensory loss (pure motor stroke)

\* Clinical features may be less than described due to the arterial occlusion being only a branch and not the entire artery or the existence of good collateral circulation minimizing the size of the infarction.

puted tomography (CT) scans are excellent for detecting a hemorrhagic stroke but often appear normal for 6 to 24 hours following an acute ischemic stroke. Subtle effacement (loss of boundaries) of sulci is the earliest sign, followed by development of a hypodense region due to development of cytotoxic and vasogenic edema (see Chapter 3, “Common Neurologic Tests”). In general, the larger the stroke the earlier it becomes visible on neuroimaging. MRI is the most sensitive neuroimaging method used to detect an ischemic stroke. While conventional MRI may appear normal for several hours, diffusion-weighted MRI will show an area of hyperintensity in

the territory of the infarct within 4 hours. Diffusion-weighted MRI scans are helpful for distinguishing an acute stroke from older strokes that are not hyperintense. Within 8 hours, edema from the infarction appears hyperintense on T2-weighted images and hypointense on T1-weighted images. MRI is sensitive for small lacunes and infarctions in the brainstem and cerebellum that may be missed by CT. In a patient with a lacunar stroke it is common to identify other older lacunes that were clinically silent.

Several tests are used to determine the cause of the stroke. Cerebral arteriography and MRA or CT angiography can identify medium-to-large-diam-



**Figure 9-2** Arterial supply of the brain. (a) Major vessels. (Continues)

eter stenotic or occluded arteries in the neck and head. Extracranial Doppler ultrasonography examination of the carotid artery in the neck also detects narrow or occluded vessels. Transthoracic or transesophageal echocardiogram can detect clots or masses within the heart, vegetations on heart valves, immobile heart segments, and cardiomegaly, which point to a cardioembolic source. Cerebrospinal fluid examination can indicate vasculitis and CSF culture may determine an infectious etiology. A variety of blood tests can look for coagulopathy or vasculopathy.

### Principles of Management and Prognosis

Treatment goals of the acute ischemic stroke are to (1) minimize the size of the stroke, (2) maximize

the extent of functional recovery, and (3) minimize the risk of subsequent strokes.

Patients with moderate-to-severe strokes require hospitalization and monitors. Electrocardiogram tests detect accompanying myocardial infarction or cardiac arrhythmias and blood pressure checks monitor for hypotension or severe hypertension. Pulmonary monitoring with pulse oximetry is important, as hypoxia can worsen symptoms. Fevers and hyperglycemia worsen stroke outcomes.

Only one drug, intravenous recombinant tissue plasminogen activator (rt-PA), has been shown to improve the outcome of acute ischemic strokes. rt-PA administration offers no immediate benefit, but produces better outcome at 3 months post-stroke. Disadvantages of this drug are considerable,

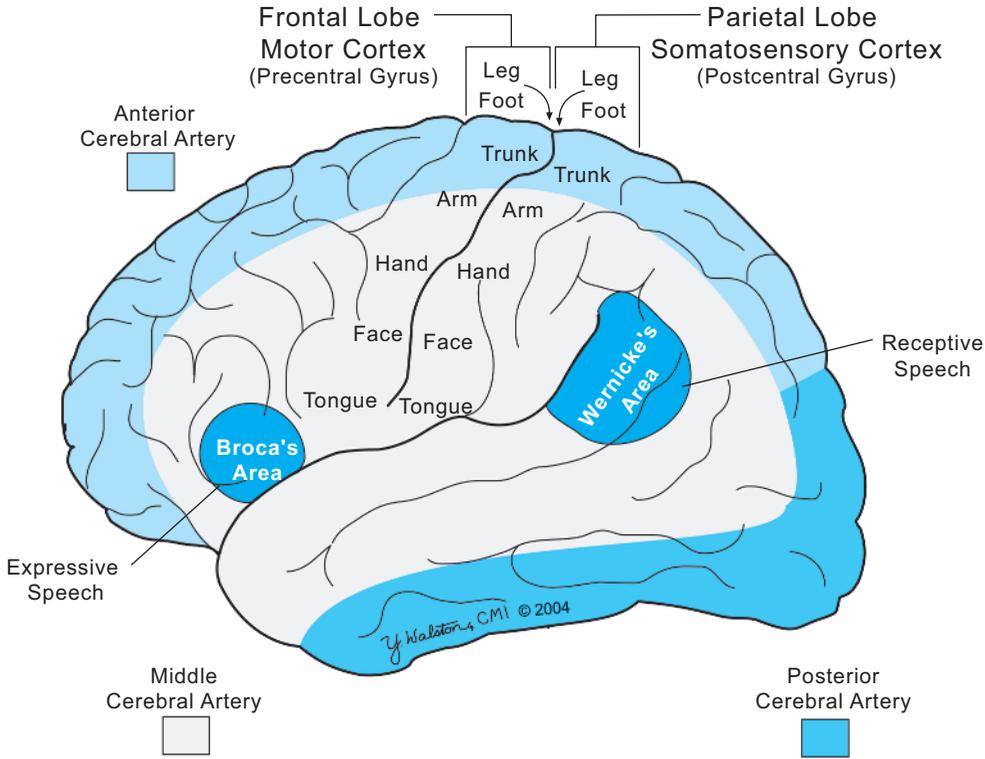


Figure 9-2 (Continued) (b) Vascular territories.

as patients must meet strict entry criteria, including (1) absence of blood on a CT scan, (2) a clinically small-to-moderate-sized stroke, (3) no history of recent myocardial infarction, gastrointestinal bleeding, surgery, or anticoagulation, and (4) reliable onset of stroke symptoms within 3 hours of rt-PA dose. Thus, many patients do not meet criteria; rt-PA carries a significant risk of intracerebral or systemic bleeding if the criteria are not followed.

Patients should begin rehabilitation as soon as they are physically and mentally able to participate. Patients with Broca's aphasia benefit from speech therapy first to improve communication by gesturing and later by speaking. Patients with motor weakness need training in transferring, dressing, standing, and eventually walking. Since 20% of patients develop venous thrombosis in the paretic leg, subcutaneous heparin should be administered until the patient begins ambulating. Most major strokes cause dysphasia of both liquids and solids. Frequently a nasogastric feeding tube

or gastrostomy is needed to maintain adequate nutrition until spontaneous recovery of swallowing occurs up to 2 months later. Patients lacking a good cough reflex are at risk for aspiration pneumonia.

Natural recovery from stroke occurs over 3 to 6 months. In general, 70% of motor recovery occurs in the first month and 90% occurs by 3 months. Recovery of speech is slower, with 90% recovery by 6 months. In hemiparetic patients, 80% walk again but only 10% regain full use of the paretic hand. Factors associated with a good recovery include young age, mild stroke severity, high level of consciousness, previous independence, living with a partner, high frequency of social contacts, and positive mood. The latter factors suggest patient motivation is important in recovery.

Prevention of subsequent strokes aims at identifying and treating the cause of the stroke, lowering modifiable risk factors, and taking oral platelet aggregation inhibitors such as daily aspirin, clopidogrel, or dipyridamole. Warfarin has not been

shown to be better than aspirin in preventing strokes unless the patient has a cardiac cause for the stroke, such as atrial fibrillation, mechanical valve failure, mural thrombus or severe cardiomyopathy. Such cardiac patients should be placed on chronic warfarin therapy and maintained at an International Normalized Ratio (INR) of 2 to 3. Patients with anterior circulation strokes and a corresponding high-grade (70%–99%) carotid artery stenosis may be considered for carotid endarterectomy by a surgeon who has a low complication rate (morbidity and mortality <3%).

## **Transient Ischemic Attacks**

### **Introduction**

A transient ischemic attack (TIA) is the sudden onset of monocular visual loss or focal neurologic symptoms that stem from one vascular territory and completely clear within 24 hours. The annual incidence in adults is 200 to 800 per 100,000. It is uncommon for a medical professional to witness a TIA, and the diagnosis usually is made from the patient's history. However, studies in which physicians examined patients during a potential TIA report that only 2/3 of the events represented a true TIA. The significance of a TIA lies not in the event but in the fact that a TIA portends a future stroke. Five-year follow up studies find there is a 30% risk of developing a stroke.

### **Pathophysiology**

Although incompletely understood, a TIA likely results from brief occlusion of a cerebral or central retinal artery as a platelet embolus lodges in the artery and rapidly breaks up, or by transiently altering circulation dynamics and perfusion through a tightly stenotic artery. By definition, diffusion-weighted MRI scans are normal and no evidence of an infarction is found at autopsy.

### **Major Clinical Features**

TIAs symptomatically fall into 3 large groupings based on involvement of the (1) ophthalmic artery, (2) middle cerebral artery, or (3) verte-brobasilar artery. Transient monocular blindness, or amaurosis fugax, results from transient occlu-

sion of the ophthalmic artery. This produces a painless, brief (minutes) sudden loss of sight involving all or part of the visual field of one eye. The visual loss is commonly described as a curtain drawn upwards or downwards over one eye that persists for minutes and then slowly reverses itself to restore vision. Permanent loss of vision is rare. Fundoscopic exam of the retina is usually normal. Patients should not have bilateral visual loss or see lights flickering in the eye when it is closed. The latter suggests a migraine aura.

TIAs involving the middle cerebral artery commonly present with sudden, painless onset of contralateral limb weakness (hemiparesis or monoparesis) and partial loss of touch and temperature sensation in the involved limbs. If the middle cerebral artery in the dominant hemisphere is affected, patients often become aphasic.

TIAs involving the verte-brobasilar system most commonly produce vertigo, ataxia, diplopia, dysarthria, and blurred vision in both eyes but rarely cause isolated vertigo or loss of consciousness. By definition, a TIA must last less than 24 hours and leave no residual deficit. However, most TIAs resolve within 6 hours, and often by 20 minutes.

### **Major Laboratory Findings**

Workup of a patient with a TIA to establish the cause should be performed as rapidly as possible. The plan follows the outline presented for an ischemic stroke, with attention drawn to the carotid artery and heart. The most common lesion is ipsilateral stenosis (70%–99%) of the internal carotid artery at the bifurcation from the common carotid artery. However, for many TIAs the cause is not found.

### **Principles of Management and Prognosis**

Treatment for most patients involves administration of platelet aggregation inhibitors beginning with daily aspirin and advancing to clopidogrel or dipyridamole if the patient does not tolerate aspirin or continues to have TIAs. Use of daily aspirin has been shown to reduce the risk of stroke by 13–20% in high-risk patients and 5% in the general population. For patients with a tight internal carotid stenosis, carotid endarterectomy by a surgeon who has a low complication rate should be considered.

## Hemorrhagic Strokes

### Overview

Intracranial hemorrhages occur in three intracranial spaces: intraparenchymal/ventricular, subarachnoid, and subdural/epidural. Subdural hematomas are discussed in Chapter 18, “Traumatic Brain Injury and Subdural Hematoma.” The significance of blood in the subarachnoid space is not that it causes immediate clinical symptoms (headache, stiff neck, etc.) but that it often comes from a ruptured aneurysm that causes life-threatening parenchymal damage.

## Spontaneous Intracranial Hemorrhage

### Introduction

Nontraumatic intracerebral hemorrhage is bleeding into the brain parenchyma that may extend into the ventricles and rarely into the subarach-

noid space. In the United States each year an estimated 45,000 people experience an intracerebral hemorrhage, with an annual incidence of 20/100,000. Intracerebral hemorrhage is more common in men, African Americans, and Japanese. Spontaneous intracerebral hemorrhages account for only 10% of all strokes, but have the highest mortality rate.

Primary intracerebral hemorrhage represents 85% of cases and results from spontaneous rupture of small arteries damaged by hypertension or amyloid angiopathy. Secondary intracerebral hemorrhages occur from arteriovenous malformations, bleeding tumors, or impaired anticoagulation.

### Pathophysiology

Intracerebral hemorrhages (hematomas) most commonly occur in the cerebral lobes, basal ganglia, thalamus, pons, and cerebellum (Figure 9-3). The bleeding results from the rupture of small penetrating arteries originating from the basilar artery or the anterior, middle, or posterior cerebral

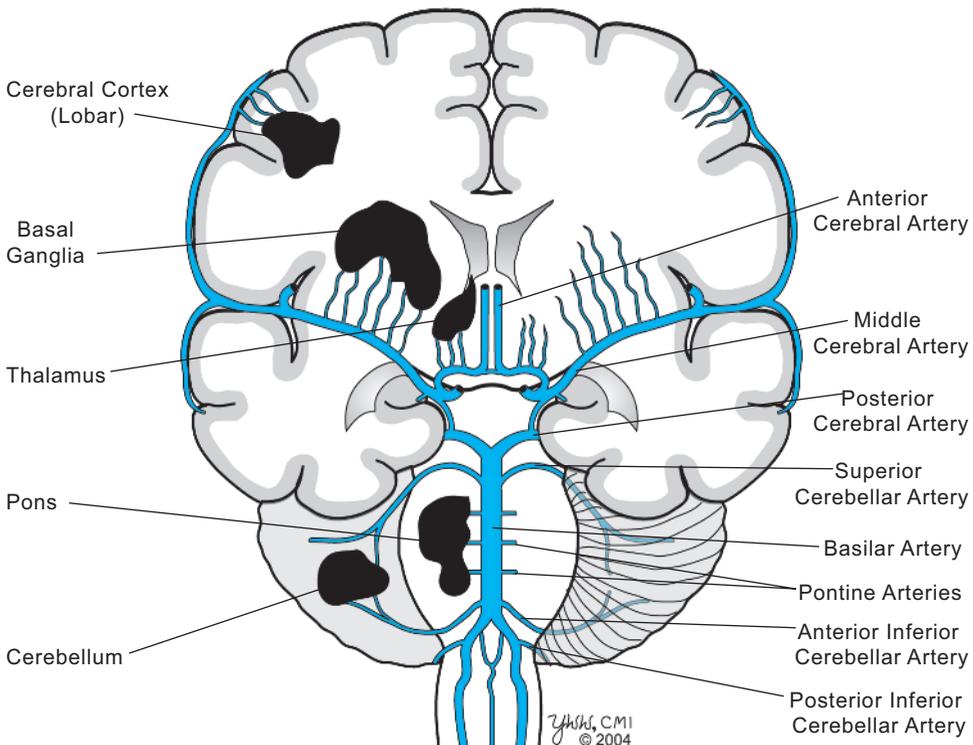


Figure 9-3 Common sites of intracerebral hemorrhages.

artery. Degenerative changes in the vessel wall media and adventitia develop from the chronic hypertension or from deposition of  $\beta$ -amyloid protein in amyloid angiopathy, particularly at or near bifurcations of affected arteries.

Following vessel rupture, blood under arterial pressure rapidly flows into adjacent brain areas. In the basal ganglia the blood disrupts the gray matter and spreads into the ventricles and into the adjacent cerebral white matter. When the rupture develops in a cerebral lobe, it spreads between planes of white matter, leaving areas of relatively intact neural tissue. The bleeding stops by tamponade within 30 minutes in most patients but in 20% the hematoma continues to expand for several hours.

The surrounding compressed brain develops vasogenic edema from release and accumulation of osmotically active clot proteins and cytotoxic edema from compression of surrounding blood vessels, producing secondary tissue ischemia. Within days macrophages and neutrophils accumulate in the surrounding brain to slowly invade the clot and remove blood products over several months. In survivors, months later there is only a small cavity whose orange-stained walls contain hemosiderin-laden macrophages.

Unfortunately, in over 25% of patients the mass from the blood clot and surrounding cerebral edema produces immensely increased intracranial pressure, leading to secondary brain herniation and death with hours to a few days.

### Major Clinical Features

The most common hemorrhage locations are the putamen, thalamus, and caudate (60% of total). These patients may suddenly become aware of “something wrong” followed minutes later by progressive depression of consciousness, vomiting, headache, contralateral hemiparesis, and abnormal eye movements. Signs of a lobar hemorrhage depend upon the lobe involved. A cerebellar hemorrhage usually begins in the dentate nucleus, with blood expansion into one cerebellar hemisphere producing headache, ipsilateral limb ataxia, vertigo, and vomiting without limb weakness.

Patients with amyloid angiopathy are usually over age 70 years and 30% have an associated progressive dementia. Most patients experience a lobar hemorrhage.

### Major Laboratory Findings

The CT scan establishes the diagnosis by the presence of an acute intracerebral hemorrhage (Figure 9-4). Secondary findings include surrounding cerebral edema, intraventricular hemorrhage, and findings of brain herniation (see Chapter 18, “Traumatic Brain Injury and Subdural Hematoma,” for details).

### Principles of Management and Prognosis

The goals of management are to improve survival from the acute hemorrhage, identify the etiology, and prevent future bleeds. The acute management of an intracerebral hemorrhage is particularly challenging. Patients often require early intubation and placement on a ventilator to control the airway, ensure sufficient oxygenation, and prevent tracheal aspiration. Frequent monitoring of vital signs and cardiac status are needed as patients often deteriorate in the first 24 hours. Cardiac arrhythmias may develop that require treatment. Seizures can occur in the first 24 hours and should be treated vigorously with anticonvulsants. A seizure raises intracranial pressure and increases the risk of brain herniation.



**Figure 9-4** Computed tomography scan of acute intracerebral hemorrhage in the left thalamus. (Courtesy of Blaine Hart, MD)

If the patient develops signs of brain herniation, repeat CT scans can determine whether new bleeding has occurred or there is obstructive hydrocephalus. Attempts to surgically remove the blood clot are controversial, except in a cerebellar hemorrhage. Little evidence exists that surgery improves quality or duration of survival. However, a moderate to large cerebellar hematoma is a surgical emergency, as removal of the hematoma carries a significant improvement in mortality and morbidity.

Patients who survive that acute phase should be evaluated for the etiology of the bleed. This may require a cerebral arteriogram to diagnose an aneurysm or arteriovenous malformation and MRI with gadolinium to identify a hemorrhagic tumor. Surgical removal of an arteriovenous malformation may be indicated.

Rehabilitation of surviving patients aims at improving limb strength, gait, and speech. Control of the hypertension is essential. However, patients with a hypertensive hemorrhage seldom experience a second hemorrhage. Prevention of rebleeding in patients with amyloid angiopathy is presently impossible and patients have a recurrence rate of 10% per year. Rebleeding from arteriovenous malformations ranges up to 18% per year.

The overall 1-year survival rate from an intracerebral hemorrhage is 40%. Neurologic sequelae are typically less severe and infrequent compared with a similar-sized ischemic stroke because neuronal tissue was compressed by the hemorrhage and less destroyed.

## Saccular Aneurysms

### Introduction

Subarachnoid hemorrhage (SAH) is the presence of blood in the meninges and CSF. Head trauma, the leading cause of SAH, is discussed in Chapter 18. Excluding trauma, the annual incidence of spontaneous SAH is 10/100,000 and accounts for 3% of all strokes. Spontaneous SAH is uncommon in infants and children, has a mean age of onset in the sixth decade, and is rare in elderly adults over age of 75 years. Women outnumber men 3:2, and African Americans outnumber caucasians 2:1.

At least 85% of SAH is due to rupture of a saccular (berry) or fusiform aneurysm. Saccular

aneurysms are little outpouchings at bifurcations of mid-sized cerebral blood vessels, while fusiform aneurysms are dilated elongated segments of the vessel. Saccular aneurysms rupture much more often than fusiform aneurysms. The remaining causes include superficial arteriovenous malformations of the brain and spinal cord and SAH in which no etiology is identified.

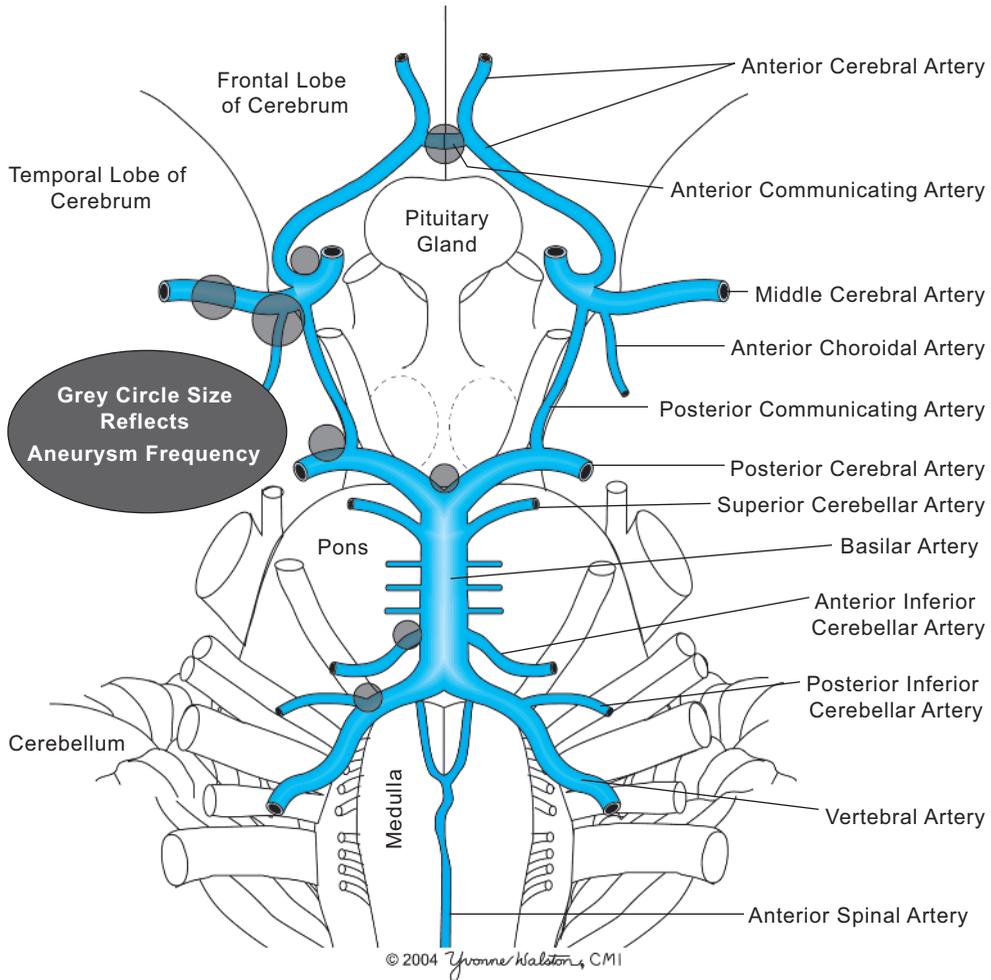
Major risk factors for rupture of an aneurysm include hypertension, smoking, heavy alcohol consumption, and a positive family history. Of patients with SAH, 10% have a positive family history, and first-degree relatives have a 5-fold risk.

### Pathophysiology

Autopsy studies estimate the prevalence of unruptured saccular aneurysms at 1%–2%, with 30% of these patients having multiple aneurysms. The location of saccular aneurysms is mainly at the bifurcation of larger vessels or at sites where disturbances of blood flow are generated, such as the anterior and posterior communicating arteries (Figure 9-5). The most common locations are the posterior communicating artery (40%), anterior communicating artery (20%), and bifurcation of the middle cerebral artery (15%). Except for a few hereditary diseases, patients with cerebral aneurysms do not have systemic aneurysms.

The pathophysiology by which saccular aneurysms develop is incompletely understood. Evidence points to development of the aneurysm in adulthood, as children seldom experience a ruptured aneurysm and autopsy studies of infants and children rarely find aneurysms. The origin of the aneurysm is just distal to a bifurcation where there are high shear forces. The aneurysm wall is characterized by (1) reduction of collagenous fibers, (2) atrophy of tunica media, and (3) loss of internal elastic lamina in addition to the expected absence of external elastic lamina. The sac of a small aneurysm is reduced to a single layer of endothelial cells and a thin fibrous layer. The histologic appearance of the artery wall before and after the aneurysm is normal. The role of genetic factors in the pathogenesis is unclear.

The risk of bleeding from an aneurysm increases considerably in those larger than 5-mm diameter. Patients with multiple aneurysms also are at higher risk of rupture.



**Figure 9-5** Distribution of saccular aneurysms.

### Major Clinical Features

Sudden, explosive headache, the cardinal feature, develops within seconds of a rupture. However, in patients presenting to an emergency room with this description, only 10% prove to have an SAH. The others are due to a “thunderclap” headache or migraine headache. Vomiting occurs in 70%. A period of unresponsiveness occurs in over half the patients and focal neurologic signs occur in 1/3 of patients. Common neurologic signs are cranial nerve palsies, including dilated pupils, disconjugate gaze, facial weakness, dysphagia, and dysarthria and hemiparesis. Seizures occur in 5% of patients. Neck stiffness usually develops hours after the bleed. Papilledema from increased

intracranial pressure is commonly seen on fundoscopic exam after 12 hours.

Occasional giant and fusiform aneurysms produce neurologic deficits by mass effect and may cause a CN III palsy or other cranial nerve deficits.

### Major Laboratory Findings

The diagnosis of SAH is best made by CT, which is widely available, rapidly performed even in a restless patient, and identifies blood in the subarachnoid space over 80% of the time. The characteristic hyperdense appearance of extravasated blood in the basal cisterns is the most common finding (Figure 9-6). Collections of extravasated



**Figure 9-6** Computed tomography scan of subarachnoid hemorrhage. The arrow denotes the hyperdense blood outlining the basilar cisterns. (Courtesy of Blaine Hart, MD)

blood elsewhere may suggest the site of the bleeding aneurysm. In 30% of patients, there is also an intraparenchymal hematoma due to rupture of the aneurysm upward into the brain. CT only detects bloody CSF when there is an RBC concentration of greater than 0.5%. After 8 hours, CSF exam demonstrates blood in all tubes and xanthochromia (yellow color) of the supernate, establishing the diagnosis in the few patients missed by CT. MRI helps to detect an SAH more than several days old.

Several methods exist to identify the location of the aneurysm and whether other aneurysms coexist. The gold standard is four-vessel catheter angiography, but this method is time consuming, difficult to perform on a sick patient, and carries a complication rate of rebleeding in 2%–5%. CT angiography using contrast media is becoming popular because it is faster, safer, and has a sensitivity of 90% compared with arteriography. Because MRA is slower and difficult to perform in a patient on a ventilator, it is less helpful.

**Principles of Management and Prognosis**

The goal is to maximize the quality of survival from the acute SAH and to eliminate the aneurysm, thus preventing rebleeding.

Patients are often classified as to severity and prognosis based on the Glasgow coma scale and other scales (Table 9-4). Patients should be placed in an intensive care unit as they often deteriorate during the first day. If mental status and breathing deteriorate, intubation and mechanical ventilation is required. Blood pressure should be carefully controlled. Pain should be controlled with narcotics.

Secondary cerebral ischemia develops in 1/3 of patients, often after several days and continuing into the second week. This ischemia can lead to secondary infarction. Arterial vasospasm (reversible narrowing of a cerebral vessel) often occurs 4 to 21 days after the bleed but does not always produce recognizable cerebral ischemia symptoms and infarctions may develop without corresponding arterial vasospasm. Nevertheless, daily administration of a calcium-channel blocker, nimodipine, from bleeding onset is associated with a modest, but significant, reduction in secondary ischemia and improvement in outcome.

Rebleeding from the aneurysm is a serious problem. Rebleeding within 24 hours of initial bleed occurs in 15% of patients. After survival of 1 day, 1/3 of patients will rebleed over the next 4 weeks, with the daily risk of bleeding being about

**Table 9-4** General Grading Systems for Ruptured Saccular Aneurysms\*

Grade	Clinical Characteristics
1	Alert, minimal headache, slight neck stiffness, and no neurologic deficit
2	Alert, moderate-to-severe headache, stiff neck, and no neurologic deficit other than cranial nerve palsy
3	Drowsiness and mild confusion with mild neurologic deficit
4	Semicoma, moderate-to-severe hemiparesis, and possible early decerebrate rigidity
5	Deep coma, decerebrate rigidity, and moribund

\* Includes Hunt Hess and Botterell and Loughheed scales.

equal. Surgical obliteration of the aneurysm has been the mainstay of treatment for decades. The surgeon is often faced with a dilemma. Operating on a comatose patient with brain edema is technically difficult and carries a considerable surgical risk of death. However, waiting 1 to 2 weeks for the brain swelling to reduce and the patient to clinically improve carries the increased risk of the aneurysm rebleeding. Studies have not identified an ideal time for surgery, but many surgeons wait until the patient's level of consciousness improves. In recent years, endovascular techniques enable placement of a detachable spring coil into the aneurysm via an arterial catheter, which triggers aneurysm clotting. While this technique has promise for select patients, the overall outcomes have been similar to surgical clipping. After 1 month, the risk of rebleeding from an unclipped aneurysm is 1% per year for 4 years and then falls much lower.

The prognosis of a ruptured saccular aneurysm is poor. Overall, 1/3 of patients die from the acute bleed and 2/3 of survivors are left with considerable neurologic sequelae and a diminished quality of life. Poor prognostic signs include grades 4 or 5 on the aneurysm grading scales, scores of 3 to 6 on

the Glasgow coma scale, presence of intracerebral hematoma, development of hydrocephalus, and rebleeding.

## RECOMMENDED READING

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- Brott T, Bogousslavsky J. Treatment of acute ischemic stroke. *N Engl J Med* 2000;343:710–722. (Reviews how ischemia damages neurons and the treatment options in an acute stroke.)
- Johnston SC. Transient ischemic attack. *N Engl J Med* 2002;347:1687–1692. (Good review, with focus on treatment.)
- Qureshi AI, Tuhrim S, Broderick JP, et al. Spontaneous intracerebral hemorrhage. *N Engl J Med* 2001;344:1450–1460. (Current review of causes and management options.)
- Staph C, Mohr JP. Ischemic stroke therapy. *Annu Rev Med* 2002;53:453–475. (Current review of clinical picture, workup, and treatment options.)
- van Gijn J, Rinkel GJE. Subarachnoid haemorrhage: diagnosis, causes and management. *Brain* 2001;124:249–278. (Excellent review of all causes, with attention to saccular aneurysms.)

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## 10 DISORDERS OF MYELIN

### *Myelin*

#### Overview

Myelin is produced in the PNS by Schwann cells and in the CNS by oligodendrocytes. Both cells are embryologically derived from the neural crest. Each Schwann cell myelinates a single 1-mm segment of a PNS axon while each oligodendrocyte myelinates as many as 60 CNS axon segments. At birth, PNS myelination is almost complete, but CNS myelination continues after birth for a decade. In the PNS, loss of Schwann cells triggers regeneration of new Schwann cells, which then remyelinate the demyelinated axon. PNS remyelination is characterized by shorter-length intervals of myelin that have fewer whorls of compact myelin. Nevertheless, remyelination often results in return of normal nerve function. Remyelination can occur in the CNS but does so to a far lesser extent.

Myelin serves several important functions. A key function is to house axons and to provide for the axons' hollow tubular channels of extracellular matrix. In the PNS, unmyelinated axons are surrounded by Schwann cell cytoplasm, but in the CNS oligodendrocytes do not wrap around unmyelinated axons. Myelin provides physical

strength to the axon. It also serves to insulate the axon from environmental toxins and prevents ephaptic transmission (direct axon-to-axon electrical transmission without a synapse). In addition, myelin allows saltatory conduction (the action potential moves down a myelinated nerve by jumping from node of Ranvier to node of Ranvier), increasing nerve conduction velocity as much as 100-fold. An unmyelinated peripheral sensory nerve has a conduction velocity of 0.5 to 1.0 m/s. A myelinated peripheral motor nerve conducts at 60 to 80 m/s. Myelination allows more efficient impulse propagation, requiring less energy. As such, myelinated axons can conduct at much faster frequencies for longer periods of time than unmyelinated axons.

Myelin contains about 70% lipid and 30% protein compared with normal cell membranes, which have only about 40% lipid. Some myelin proteins, such as myelin basic protein, myelin-associated glycoprotein, and myelin oligodendrocyte glycoprotein, are specific to myelin, can become immunogenetic, and may be the target of immune-mediated myelin damage.

Demyelinating diseases occur when the disease process primarily involves myelin sheaths, Schwann cells, or oligodendrocytes. Thus there is damage to myelin sheaths with relative sparing of

the underlying axon. Diseases such as strokes that destroy both myelin and axons are not considered demyelinating diseases. The disease process may involve CNS myelin, PNS myelin, or both. Causes of demyelinating disease include genetic (Charcot-Marie-Tooth neuropathy), toxic (diphtheric polyneuropathy), infectious (progressive multifocal leukoencephalopathy), immune-mediated (Guillain-Barré syndrome), and unknown (multiple sclerosis).

There are four major mechanisms of demyelination: (1) death of oligodendrocytes or Schwann cells, (2) interference with myelin synthesis, (3) interference with myelin turnover, and (4) immune-mediated destruction of myelin.

Signs and symptoms of demyelination are due to dysfunction of the underlying axon. In general, the longer the myelinated nerve tract, the greater the probability that a demyelinating disease will disrupt its function. In the CNS, tracts commonly involved include the corticospinal tract (weakness and spasticity), spinothalamic tract (sensory loss), visual pathway (visual disturbance), and spinocerebellar pathways (ataxia). Of note, demyelinating diseases seldom produce the signs of gray matter disease, such as early dementia and aphasia, basal ganglia deficits (parkinsonism or chorea), or seizures. In the PNS, motor and sensory (vibration sense) myelinated nerves are often mildly involved. Similarly, the sensations of pain and temperature (unmyelinated axons) are seldom impaired. In general, genetic and toxic causes of demyelination usually produce symmetrical signs, while immune-mediated and infectious causes of demyelination are often asymmetrical.

## Multiple Sclerosis

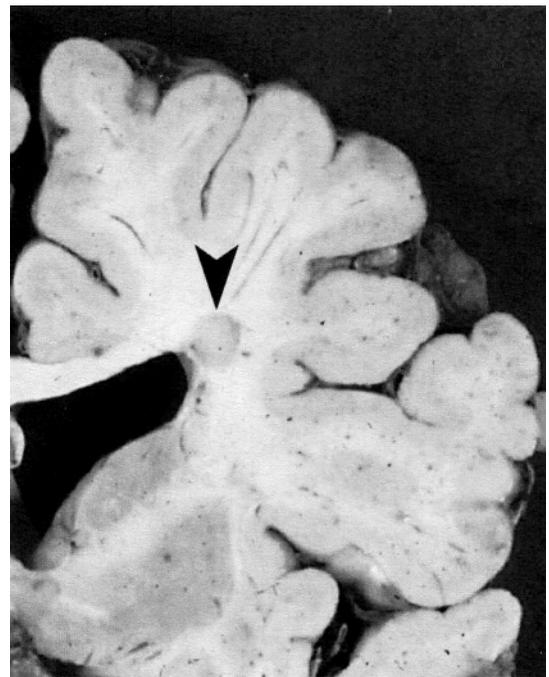
### Introduction

Multiple sclerosis (MS) is an enigmatic, relapsing, and often eventually a progressive disorder of CNS myelin. The classical definition of MS requires dissemination of CNS white matter lesions in time (multiple attacks) and space (involving different areas of CNS white matter). There is a female predominance of about 2:1. The disease usually begins in the third decade of life. Over 300,000 adults in the United States have the disorder. However, the prevalence varies from less than

5/100,000 to 30/100,000 adults around the world, with higher prevalences occurring the further north or south one lives from the equator.

### Pathophysiology

The pathologic hallmark of MS, the demyelinated plaque, consists of a well-demarcated hypocellular area characterized by the loss of myelin, relative preservation of axons, and the formation of astrocytic, glial scars (Figure 10-1). The lesions are usually oval and have a small- or medium-sized blood vessel near the center. Inflammatory cells (mainly lymphocytes and macrophages) are typically perivascular in location, but may infiltrate the lesion diffusely. Some plaques demonstrate partial remyelination while others do not. Plaques may occur anywhere in the CNS but not in the PNS. Common locations for plaques include the white matter of optic nerves, surrounding lateral ventricles, corpus callosum, brainstem, cerebellum, and spinal cord. Lesions involve both hemispheres and distribute asymmetrically. Recent studies suggest that there are 4 pathologic forms of MS. The 2 most-common forms appear to display primary



**Figure 10-1** Pathologic specimen showing multiple sclerosis plaques. (Courtesy of Mario Kornfeld, MD)

damage to CNS myelin (the first form mediated by antibody, complement, and immune cells and the second mediated only by immune cells), while the other two forms appear to incur primary damage to the oligodendrocytes. Whether the 4 forms have different etiologies is unknown, but in the future may direct patient treatment.

The cause of MS remains mysterious. Extensive searches for an infectious agent or genetic cause have yet to identify a likely etiology. While there is mounting evidence that damage to CNS white matter develops from an immune-mediated process, the initial inciting antigen and how the immune process is maintained at irregular intervals for years remains unclear. Nevertheless, our most-successful treatments have been directed against modifying the immune process.

### Major Clinical Features

The clinical features and rate of MS progression vary considerably from patient to patient. Neuroimaging has shown that plaques often appear in “silent” brain areas without producing clinical signs. In the early phase of MS, clinically apparent attacks develop about once or twice a year. The onset occurs over 1 to 2 days and does not have an identifiable trigger. Common clinical signs occur from damage to long CNS myelinated tracts. Thus, MS patients often develop hemiparesis or monoparesis (corticospinal tract), unilateral visual loss (optic nerve), sensory loss (posterior columns or spinothalamic tracts), ataxia (cerebellum or cerebellar pathways), and neurogenic bladder or paraparesis (spinal

cord). Patients often complain of worsening of their symptoms in hot weather or when they are febrile.

Spontaneous clinical return of function usually occurs within a month. In the relapsing–remitting form of MS (80% of patients), full return of function prevails but over time, attacks may leave some permanent dysfunction (Figure 10-2). Return of clinical function occurs when the demyelinated portion of the axon converts from permitting only saltatory conduction requiring myelin to an axon segment that has continuous conduction, like unmyelinated axons (Figure 10-3). Thus the conduction velocity slows but function returns. When brain temperature rises, some continuous-conducting axons develop temporary conduction blocks, which explain the worsening of a patient’s symptoms in hot weather. Remyelination of demyelinated axons in a plaque is so limited that it probably does not result in significant clinical improvement. Permanent loss of function is associated with loss of the underlying axons.

After 5 to 10 years, relapsing–remitting patients often develop a slowly progressive illness called secondary progressive MS (Figure 10-2). A few percent of patients slowly progress without acute attacks (primary progressive MS). Over 30 years, about 1/2 of MS patients will develop sufficient ataxia or spasticity to require a wheelchair. Life expectancy shortens only slightly.

### Major Laboratory Findings

There is no diagnostic test for MS. However, there are characteristic cerebrospinal fluid (CSF) changes

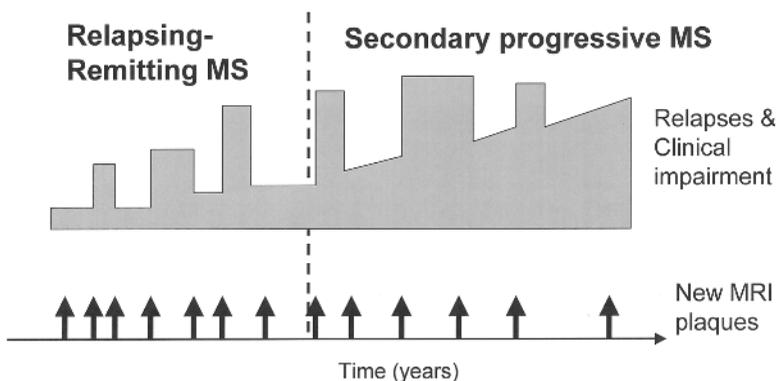
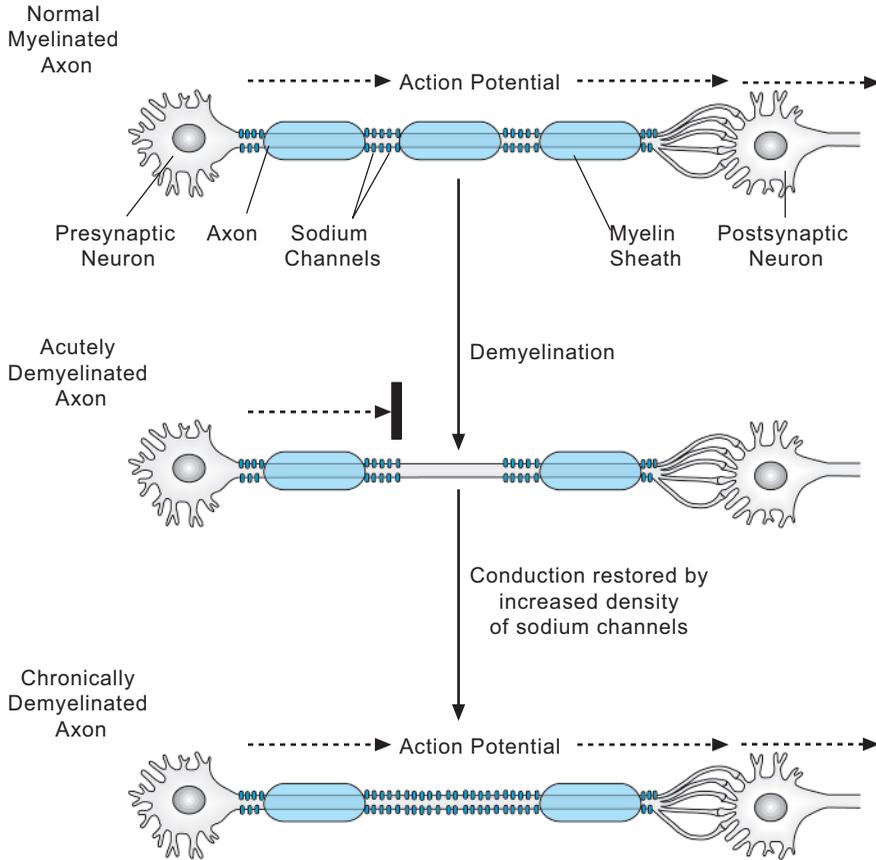


Figure 10-2 Natural history of multiple sclerosis.



**Figure 10-3** Axonal changes in acute and chronic demyelination.

that occur in most patients. The CSF usually shows an increased IgG synthesis rate (IgG index) and several oligoclonal bands. This indicates migration of B lymphocytes and plasmacytes from blood to brain plaques with subsequent local homogenous antibody production that then leaks into CSF. It is not known what antigen the MS antibody is directed against. The CSF may contain a small number of lymphocytes but should have a normal glucose level. Routine blood tests are normal.

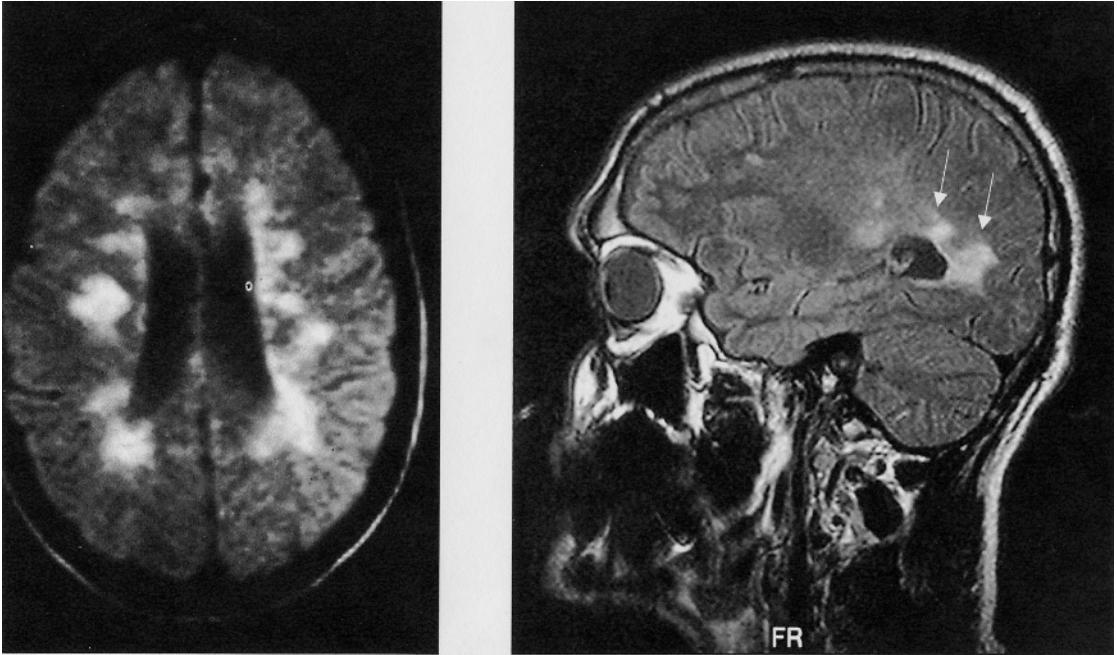
MRI scans are sensitive, but not specific, indicators for myelin plaques. FLAIR and T2-weighted MRI lesions reflect inflammation, edema, demyelination, and gliosis (Figure 10-4). T1-weighted lesions (“black holes”) often reflect marked axonal loss in the plaque (Figure 10-4). Gadolinium-enhancing lesions on T1-weighted images suggest disruption in the blood–brain barrier from active inflammation and demyelination. Neuroimaging lesions occur in the same locations found at

autopsy and are commonly seen as perpendicular ovals in the white matter around the lateral ventricles, corpus callosum, cerebellum, and spinal cord.

MS is a clinical diagnosis with laboratory support. Patients should be young adults, have at least one definite clinical attack characteristic for MS, and have definite signs or MRI lesions distributed in several areas of the white matter of the brain and the spinal cord. The clinical diagnosis is supported by the presence of CSF oligoclonal bands and increased IgG synthesis. No other diagnosis for the clinical signs should be apparent.

### Principles of Management and Prognosis

Treatment of MS is divided into treatment of acute lesions, rehabilitation of the patient with chronic disease, and prevention of future plaques. Acute relapses are often treated with short courses of high-dose corticosteroids. While spontaneous



**Figure 10-4** FLAIR magnetic resonance imaging scan of multiple sclerosis plaques. (Courtesy of Coley Ford, MD)

clinical recovery takes about 4 weeks, steroids appear to shorten the time to recovery by 1 to 2 weeks. However, steroids do not improve the extent of recovery or change the course of the disease. Chronic treatment with steroids has not been shown to prevent subsequent relapses.

Rehabilitation aims at maximizing patient functioning. Patients commonly become depressed, requiring counseling and antidepressant medication. Fatigue becomes a problem and is difficult to treat. Bladder spasticity with urinary incontinence may develop, requiring treatment. Ataxia and spasticity affect gait, balance, and coordination, interfering with activities of daily living.

Several drugs have been found effective in reducing the frequency of new lesions in relapsing–remitting MS. Interferon  $\beta$ -1b, interferon  $\beta$ -1a, and glatiramer acetate all reduce the frequency of relapses by about 30%. Serial neuroimaging studies show these drugs reduce new T2-weighted lesions by about 60%. While these drugs in short-term studies have shown a trend toward delaying progression of disability, they have not reached statistical significance. The mechanisms by which interferon and glatiramer acetate work are uncertain, but studies suggest the

drugs affect the immune-mediated attack to white matter. Both the interferons and glatiramer acetate require daily or weekly administration injections, have a moderate number of local and systemic side effects, and are expensive (about \$10,000/yr). It is currently unknown how long these drugs should be taken. Mixantrone, a chemotherapeutic drug, remains the only medication indicated for primary or secondarily progressive MS.

## Guillain-Barré Syndrome

### Introduction

Guillain-Barré syndrome (GBS) is a monophasic disease involving only myelinated nerves in the PNS. The most common form (>80% in the United States), called acute inflammatory demyelinating polyneuropathy (AIDP), appears to be due to an immune-mediated attack of peripheral myelin. Acute motor axonal neuropathy (AMAN) clinically is more severe than AIDP. The immune attack in AMAN appears directed against the PNS myelinated axon exposed at the node of Ranvier. The annual incidence of GBS in the United States

is about 1 to 2 cases per 100,000 persons. The incidence increases with age, and males slightly predominate. Patients with partial immunosuppression are at an increased risk for GBS.

### Pathophysiology

GBS occurs in the setting of an antecedent illness in about 60% of patients. Upper respiratory and gastroenterologic infections are frequent, with the most common being viruses (cytomegalovirus and Epstein–Barr) and bacteria (*Campylobacter jejuni*). It is proposed that via molecular mimicry the patient develops an immune response against the infecting agent that cross-reacts with antigens on the patient's peripheral nerve myelin or axons.

In AIDP, nerve damage results from lymphocytic immune responses against peripheral nerve myelin, with antibodies playing an unclear role. The pathology shows patchy lymphocytic infiltrates, particularly around venules and capillaries within the endoneurium, and macrophages around the myelinated nerves. Hematogenous macrophages adhere to nerve fibers, where they penetrate the Schwann cell basal lamina, extending processes that amputate myelin lamellae and “strip” myelin away from the axon. This process produces segmental demyelination. The most heavily affected part of the nerve is the proximal root. Multiple peripheral nerves are involved in a uniform and generally symmetrical fashion. Central nervous myelin is not affected. Clinical recovery occurs over weeks when the demyelination stimulates abundant Schwann cell proliferation with subsequent remyelination of the naked axonal segment. Remyelination produces short-length myelin segments that are thinner than the original myelin.

In AMAN, antibodies (especially those associated with *Campylobacter jejuni*) appear to attack axon antigens located at the internodal axolemma. In a variant of AMAN called Miller Fisher syndrome (ataxia, areflexia, and internal and external ophthalmoparesis), the responsible antigen appears to be a GQ1b-like epitope that is shared by some bacteria and axons. The nerve pathology is largely noninflammatory and dominated by wallerian-like degeneration of nerve fibers, which accounts for the poorer prognosis of AMAN. Another uncommon variant called chronic inflammatory demyelinating polyneuropathy (CIDP) appears to be an antibody-mediated

chronic disease of myelinated peripheral nerves that shares many similarities with GBS and responds to plasmaphoresis, corticosteroids, and immunosuppressive agents.

### Major Clinical Features

Flaccid weakness is the hallmark of GBS. Leg weakness is often the earliest sign but usually the weakness involves all extremities. The weakness is both proximal and distal and may also involve motor cranial nerves, producing facial weakness and trouble swallowing and chewing. About 50% of patients experience a reduced vital capacity and about 25% require ventilator assistance. The weakness progresses over 1 to 3 weeks and then plateaus. Clinical involvement of the myelinated autonomic nerve system is common and may be life threatening. Complex supraventricular tachycardias, abrupt bradycardia, and bouts of hypertension or hypotension may occur spontaneously, follow minor adjustments in posture, or occur during painful stimuli. Most patients become areflexic during the first week even if weakness is minor. Diminished vibration sense in the feet is common, but loss of touch, pain, and temperature rarely occurs. Loss of bladder or bowel control is uncommon. Mentation remains normal.

In most cases the diagnosis is based on typical clinical signs. For atypical cases, the differential diagnosis includes acute intermittent porphyria, lead poisoning, tick paralysis, diphtheric polyneuropathy, and critical illness neuropathy.

The weakness progresses over the first 1 to 3 weeks, with subsequent stabilization and recovery. In mild cases of AIDP, motor recovery can occur over a few weeks. For AIDP patients who cannot walk, ambulation often takes 4 to 6 months. In severe cases, recovery may continue for up to 2 years. In AIDP, about 85% of patients fully recover and 15% are left with minor sequelae such as loss of reflexes. In AMAN, up to 1/2 of patients are left with neurologic sequelae. Death following cardiac arrhythmias or infectious complications still occurs in 2% to 3% of patients with GBS.

### Major Laboratory Findings

Major blood tests are normal. The CSF becomes abnormal during the first week. CSF protein elevates to levels of 100 to 400 mg/dL but CSF IgG

synthesis does not increase and oligoclonal bands do not develop. The CSF has a normal glucose level and normal WBC count. If a CSF pleocytosis exists, other diagnoses such as HIV infection, poliomyelitis, West Nile viral myelitis, or meningeal carcinomatosis should be considered. Neuroimaging of the spinal cord should be normal.

Nerve-conduction study results become abnormal in AIDP by the end of the first week. Mean values for compound motor action potential (CMAP) amplitude following nerve stimulation reduces to about 25% to 50% of normal, implying conduction blockage in the majority of motor axons. The motor nerve conduction velocity reduces to 50% to 70% of normal after several weeks, reflecting the segmental demyelination. Variable evidence of muscle denervation may be found on electromyography beginning after 2 to 3 weeks. In AMAN, the motor nerve conduction velocity does not fall markedly, but the amplitude of the CMAP does, as there is widespread evidence of muscle denervation, reflecting that pathologic damage primarily occurs in axons.

## Principles of Management and Prognosis

The key to successful management is excellent nursing care. Patients usually require hospitalization and placement in a critical care setting. About 1/4 of patients require a ventilator. Cardiac monitoring is recommended because patients may be prone to severe arrhythmias that may require electrical cardioversion and medication.

Plasmaphoresis or human immune globulin is beneficial if given early in the course of AIDP. Both equally shorten the time to recovery and likely prevent progression of disease to more severe stages. In contrast, use of corticosteroids is not beneficial. Presently, it is unclear which treatments for AMAN may be beneficial. During recovery, physical therapy often improves function.

## RECOMMENDED READING

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Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;343:938–952. (*Excellent recent review of genetic and pathologic features, immunology, and treatment of MS.*)

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# 11 DISORDERS OF HIGHER CORTICAL FUNCTION

## Overview

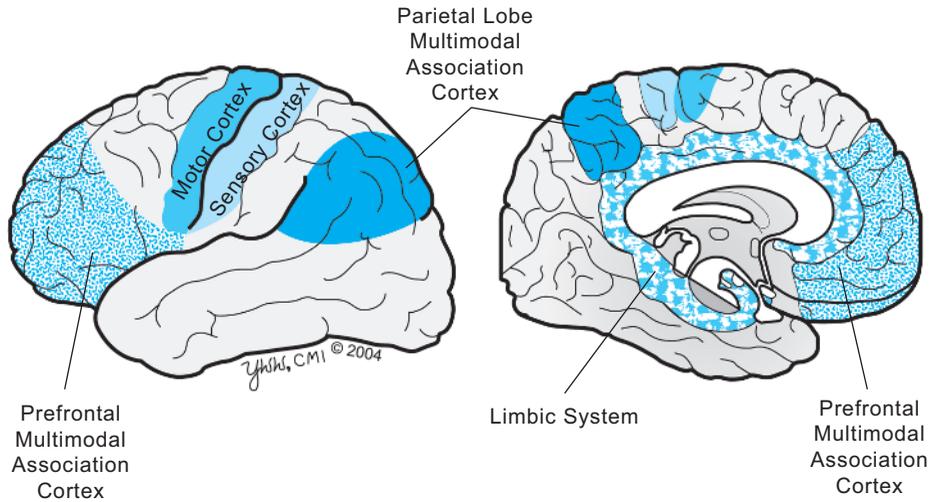
Higher cortical functions process raw sensory signals into complex concepts that can be remembered and used to create new ideas that can be formulated into action. It is the part of the brain which, for example, converts a sound (sensation) into a word, then into a sentence. This is then combined with higher-level processes such as semantic memory, which the brain integrates into an idea or thought (conception) that can be remembered, compared with other ideas, and used to create new ideas that in turn can be remembered or acted upon.

The physiology involved in higher cortical function is poorly understood, but definitely involves interaction among many cortical and sub-cortical regions, and often between both hemispheres. The two hemispheres are not equal in function, but the precise differences are not understood. The dominant hemisphere is the one most responsible for language and fine motor control functions such as writing. The left hemisphere is dominant in over 95% of right-handed individuals and in 70% of left-handed individuals.

In simple conceptualization, the cerebral cortex can be divided into 3 regions that deal with sensory information in increasing levels of complex-

ity. Visual, auditory, and somatosensory information goes to the primary sensory cortex. The unimodal association cortex refines single sensory information. The multimodal association cortex receives input from all sensory modalities and handles complex intellectual functions, such as logic, judgment, language, emotion, ambition, and imagination (Figure 11-1). Multimodal association cortices are located in the prefrontal, limbic, and parietal lobes. The prefrontal lobe is responsible for problem solving, self-monitoring, planning, mental tracking, and abstract thinking. The limbic association cortex participates in memory and emotion. The parietal association cortex is the setting for language, space orientation, complex movement, and recognition of self and the world.

Until recently, much of our understanding of higher cortical function has come from the investigation of patients with defined cortical lesions. Based on these studies, we have some understanding of the functions of specific areas. Recent studies of normal individuals using PET, fMRI, and intracortical electrical recordings are providing ideas of the normal functions of cortical areas. To the clinician, recognition of specific higher cortical function syndromes has proven helpful in anatomic cerebral localization. Below are brief descriptions of what is known about the anterior



**Figure 11-1** Higher cortical function multimodal association cortices.

prefrontal lobe, limbic/temporal lobe, and parietal lobe. In addition, there is a discussion of the clinical deficits patients may experience when lesions occur in a specific multimodal association cortex.

## Prefrontal Lobe

The prefrontal association cortex, located anterior to the motor and premotor frontal cortex, is supplied by branches of the anterior and middle cerebral arteries. Table 11-1 lists the recognized functions of the prefrontal lobe. Clinical dysfunction usually occurs when the damage is fairly large and involves both prefrontal cortices. Thus surgical removal of a considerable area of one prefrontal cortex leaves subtle deficits generally only detected with detailed neuropsychologic evaluation. In contrast, head trauma causing bilateral prefrontal lobe damage can produce considerable signs and symptoms. This occurs in part because of bilateral damage to fiber pathways that communicate between the frontal cortex and subcortical sites.

Damage to prefrontal cortices can produce such reflexes as grasp, snout, suck, and rooting. These reflexes are normal in the newborn, but disappear by about 4 months of age, presumably due to myelination of inhibitory pathways from the prefrontal cortices. The *grasp reflex* is revealed in the inability to release a grasp when an object, such as the examiner's finger, stimulates the palm. The *snout reflex* is elicited by touching the patient's lips,

causing the mouth to pucker involuntarily. The *suck reflex* is said to be positive when the patient's mouth opens involuntarily in response to an object moving toward it. The *rooting reflex* is positive when lightly stroking the side of the face produces an involuntary head turning toward the stimulation.

Table 11-1 lists the clinical features seen in patients with prefrontal cortical damage. These patients often demonstrate high impulsivity without forethought to the consequences, inability to perform several tasks simultaneously (multitasking), lack of drive to work or complete tasks, and a tendency to appear disheveled or half-dressed.

## Limbic System

The limbic system includes the limbic lobe (subcallosal area, cingulate gyrus, parahippocampus, uncus, and hippocampal formation), many nuclei of the nucleus accumbens, the hypothalamus, mamillary bodies, and the amygdala (Figure 11-2). The major arterial supply comes from the anterior and posterior cerebral arteries and anterior choroidal artery. The two major concerns of the limbic system are memory and emotion.

Consolidation of long-term memories from immediate memory (lasting seconds) and short-term memory (lasting minutes) is the basic function of the hippocampal formation. Long-term memory can be recalled days to years later. While

**Table 11-1 Major Higher Cortical Brain Areas, Normal Functions, and Syndromes**

<b>Cortical Area</b>	<b>Major Functions</b>	<b>Clinical Syndromes Seen When Area Damaged</b>
Prefrontal Lobe	Judgment Insight Foresight Ambition Sense of purpose	High distractibility Lack of foresight or insight Inability to switch from one task to another Lack of ambition Lack of sense of personal responsibility Lack of social propriety and self-monitoring
Limbic System	Short-term memory Consolidation of long-term memory Emotional response	Amnesia Akinetic mutism Flat emotional affect
Parietal Lobe	Perception of somatosensory input  Integration of all sensory data Awareness of body and its relationship to external space  Language	Cortical sensory deficits Astereognosis Agraphesthesia Poor double simultaneous sensory stimulation Visual neglect and Anton's syndrome Apraxias Construction apraxia Ideomotor apraxia Ideational apraxia Aphasias Global aphasia Broca's aphasia Wernicke's aphasia

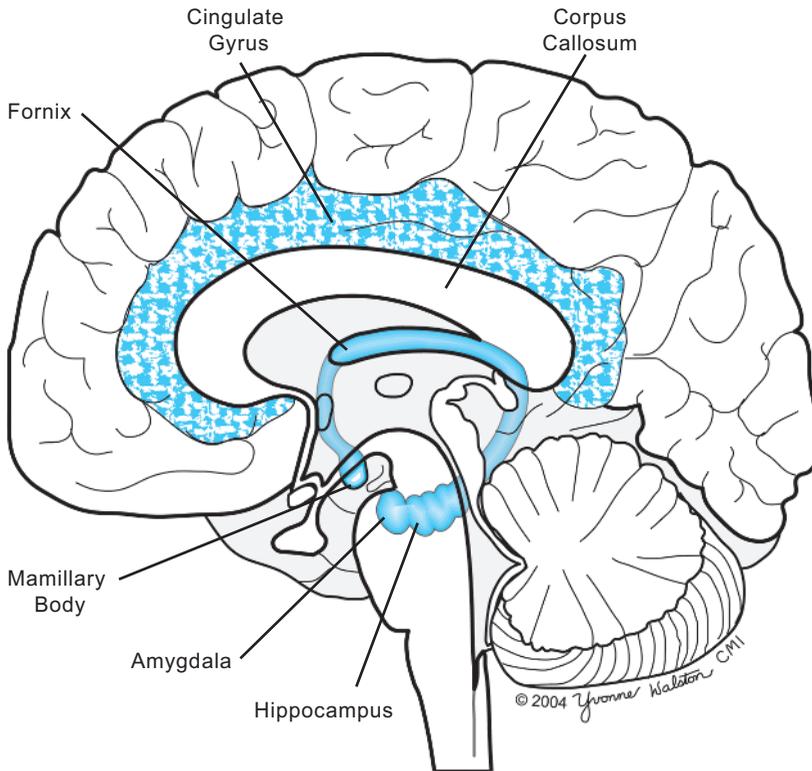
the hippocampal formation is responsible for establishing long-term memories, no single brain location appears responsible for the repository of long-term memories, although it is likely cortical. Thus no single brain lesion can eradicate well-formed long-term memories. However, extensive damage to the brain in dementia patients can be associated with impaired long-term as well as short-term memory.

Lesions that cause memory impairment are usually bilateral and may involve the hippocampal formations, dorsomedial nuclei of the thalami, or mamillary bodies. However, damage to the left temporal lobe can produce verbal memory deficits, while damage to the right temporal lobe can produce nonverbal memory deficits. The most common diseases that produce devastating memory loss are Wernicke–Korsakoff syndrome, bilateral temporal lobe contusions from head trauma, anoxia due to cardiac arrest, and advanced Alzheimer's disease.

The limbic system also participates in emotional responses. Electrical stimulation of various sites in the limbic system may produce fear or sorrow (aversion centers) or pleasure (gratification centers). Damage to the limbic system can produce varied emotional changes. Large limbic lesions often produce a flattening of emotions, presumably due to loss of both aversion and gratification centers. Bilateral damage to the anterior cingulate gyri or supplementary motor area may dramatically diminish emotional responses and produce an awake-appearing patient who is immobile, mute, and unresponsive to his or her environment (akinetic mutism).

### **Parietal Lobe**

The parietal lobe begins behind the central sulcus and extends backward and inferiorly to merge with the occipital and temporal lobes at poorly defined



**Figure 11-2** Limbic system anatomy.

boundaries. The inferior division of the middle cerebral artery principally supplies blood to the parietal lobe. The parietal lobe is a higher-order integration center whose functions are listed in Table 11-1. Electrical stimulation of most parietal lobe neurons does not evoke specific sensory or motor effects, but lesions do produce specific clinical deficits.

Patients with a lesion involving the postcentral gyrus, especially in the hand primary sensory area, usually have relatively intact perception of pain, touch, pressure, temperature, and vibration but often have “cortical” sensory deficits. *Astereognosis* is the inability to distinguish and recognize small objects based on size, shape, and texture when placed in a hand that has normal primary tactile sensory input. *Agraphesthesia* is the inability to recognize numbers or letters written on the palm. Loss of *double simultaneous sensory stimulation* is the inability to detect and localize two identical stimuli applied simultaneously and bilaterally to comparable areas on the face or limbs. For example, if the examiner touches the backs of the patient’s hands and asks him or her to identify

which side was touched, the patient will only report feeling the touch on the ipsilesional side.

Neglect syndromes cause lack of attention to the contralateral side of the body (spatial neglect) or to the contralateral visual space (visual neglect). Patients with hemiparesis due to a lesion of the motor cortex or corticospinal tract and a parietal lobe lesion may be unaware of their arm and leg paralysis (anosgnosis). Similarly, bilateral occipital lobe lesions that involve the parietal lobe may produce blindness that is denied by the patient (Anton’s syndrome). Lesions involving only the parietal lobe may produce apraxia on one side of the body in dressing and grooming (dressing apraxia). Lipstick may be applied to only one side of the lips and patients may not be able to put on a shirt or pants.

Lesions of the nondominant superior parietal lobe may give rise to disturbances of perception of two- or three-dimensional space. These patients have difficulty with route finding and reproducing geometric figures, and disturbances in organizing parts of a complex object (constructional apraxia) (Figure 11-3). A good bedside test is to ask a patient

to draw a clock with numbers and the hands showing a specific time. Patients with constructional apraxia often crowd the numbers on one side (visual neglect), may draw numbers incorrectly (6 for 9) or on the wrong side of the clock, and cannot draw the hands correctly (Figure 11-3).

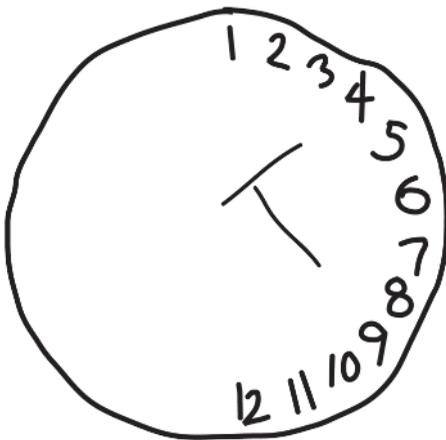
Apraxia is the inability to execute complex and previously learned skills and gestures in a person who is alert and has no weakness or ataxia that prevents the movements. Lesions of bilateral parietal lobes may produce *ideational apraxia* or impaired knowledge of what action is associated with a particular object. Often they use the wrong object for a particular function and display spatial or temporal errors. Lesions of the dominant parietal lobe most frequently produce *ideomotor apraxia* or spatiotemporal deficits imitating movements without objects. For example, the patient might use jerky vertical movement rather than smooth horizontal movements when imitating a carving movement. Apraxias involve both sides of the body, but they are tested in the ipsilesional limb to be sure that they are not due to a motor deficit.

## Aphasias

Theories of speech and language continue to evolve as no current hypothesis satisfactorily explains nor-

mal speech. Traditionally, language disorders have been divided into specific categories that originally were thought to be due to damage to focal brain regions, usually different areas of the left hemisphere in right-handed patients. With current neuroimaging, brain regions giving rise to specific types of language disorders have been found to be much larger than previously thought and show considerable overlap (Figure 11-4). Thus fine subdivisions of language currently are of limited clinical usefulness. Nevertheless, dividing language disorders into 3 major categories does have clinical usefulness (Table 11-2).

Global aphasia implies loss of all speech and language function. There is loss of comprehension of verbal and written language plus inability to communicate in speech or writing. These patients do not obey verbal commands, and cannot repeat phrases or produce meaningful speech or writing. However, some patients may express stereotypic utterances such as “OK”, “fine”, “sure”, and “no,” or express simple profanity, none of which are appropriate to the question. Most cases of global aphasia are due to large infarctions involving the central regions surrounding the Sylvian fissure and almost always produce an accompanying hemiparesis, hemisensory loss, and often a homonymous hemianopia. In general, prognosis for recovery is poor.

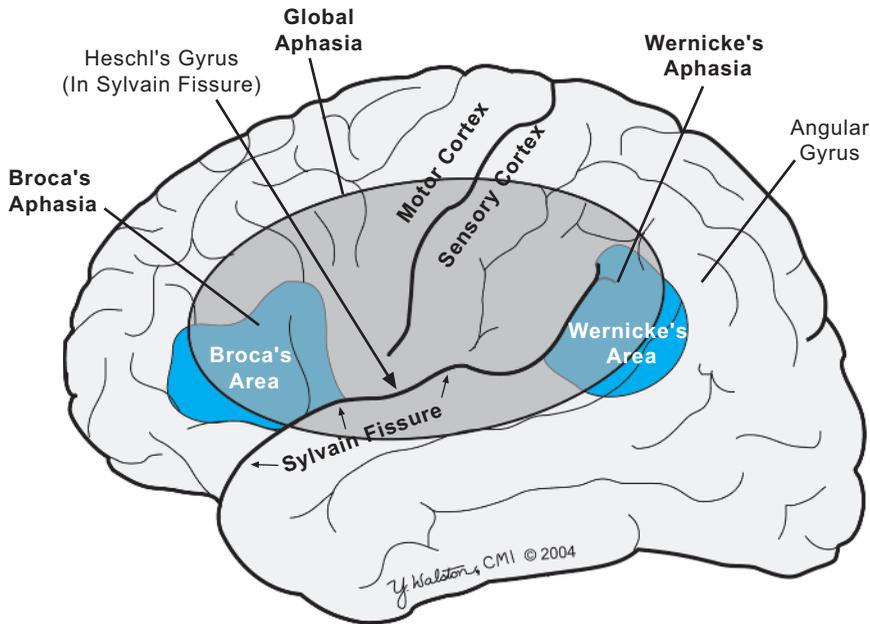


**Contralateral Neglect**



**Constructional Apraxia**

**Figure 11-3** Parietal lobe lesions causing neglect and apraxia.



**Figure 11-4** Location of brain lesions causing aphasias (left cortex).

Broca's aphasia (expressive/motor/anterior/non-fluent aphasia) implies disproportionate difficulty with formulating sentences and speaking them aloud, compared with comprehending verbal and written communication. Acutely, some patients cannot speak at all. Over time, patients express short telegraphic speech that emphasizes informational nouns and verbs and tends to be devoid of noncritical adjectives and adverbs. The speech melody is distorted, sounds more guttural, and is often explosive. Use of stereotypic utterances may occur but may not be correct responses to the question. Repetition of phrases is impaired. Because patients understand simple spoken language, they may respond appropriately or express their needs

by using nonverbal responses (miming). Lesions that produce Broca's aphasia were originally thought to be from a focal lesion in the inferior frontal area (Broca's area), but it is now recognized that larger lesions in that area can produce Broca's aphasia (Figure 11-4). Patients with Broca's aphasia from a stroke usually have an accompanying hemiparesis. Prognosis depends on the cause (worse for tumors than infarct) and lesion size. For infarction, many patients regain reasonable-to-good functional telegraphic speech over 6 months.

Wernicke's aphasia (receptive/sensory/posterior/fluent aphasia) implies severe impairment in comprehension of verbal and written communications, with the maintenance of fluent speech. Patients are

**Table 11-2 Major Aphasia Types and Their Clinical Features**

Type	Verbal Expression	Ability to Repeat	Ability to Comprehend
Broca's aphasia	Nonfluent but content, understandable with truncated phrases containing mainly informational words	Impaired	Good for simple one-step commands but impaired for complex commands
Wernicke's aphasia	Fluent but noncomprehensible with excess noninformation words and paraphasias	Impaired	Poor to absent
Global aphasia	Mute or nonfluent	Impaired	Poor to absent

usually unaware of their comprehension difficulties and may appear attentive and cooperative. The speech usually has normal melody or prosody, is pronounced clearly without effort, and is of normal to prolonged length. However, the speech content does not make sense, lacks informational words (nouns), contains excessive adverbs and adjectives, contains nonwords (neologisms), and is mispronounced or has inappropriately substituted words (paraphasias). Semantic paraphasias are errors based on the meanings of words (aunt for uncle) and literal paraphasias are errors based on sounds (hook for took). A patient with psychosis usually has an abnormal frame of reference. Thus in response to the question, “What is your name?” the schizophrenic may answer, “Jesus Christ” (implying he understood the question and answered it relative to his world), while the patient with Wernicke’s aphasia may reply, “It is a lovely, beautiful, warm, rainy day on this weekend (implying he never understood the question).

Wernicke’s aphasia patients cannot repeat phrases. Lesions commonly involve the posterior end of the Sylvian fissure and spread varying distances across the posterior half of the brain (Figure 11-4). Vascular occlusions of the posterior temporal branch and the angular branch of the middle cerebral artery in the dominant hemisphere can cause Wernicke’s aphasia without producing hemiparesis. The prognosis of Wernicke’s aphasia varies. Many recover reasonable verbal comprehension and usable appropriate speech, but the speech may continue to contain paraphasias and word-finding difficulties (dysnomia).

## Intelligence

Intelligence is a general mental capability that includes reasoning, planning, solving problems, thinking abstractly, comprehending complex ideas, learning quickly, and learning from experience. Low intelligence does not come from dysfunction of a single brain region but from dysfunction or damage of many bilateral areas of higher cortical function. Although imperfect, intellectual reasoning is usually represented by an intelligence quotient (IQ) obtained from appropriate testing instruments. An IQ score is performance on a standardized test adjusted to the individual’s chronological age. The most com-

monly used tests are the Wechsler Adult Intelligence Scale-III and Wechsler Intelligence Scale for Children-III. In general, mental retardation or dementia can be defined as IQ scores 2 standard deviations or more below the norm. In mental retardation, the patient has never had an IQ score within the norm. In dementia, it is loss of previously acquired intellect. A commonly used rapid office-screening test is called the Folstein Mini Mental Status Exam (MMSE; see Chapter 2, “Neurologic Examination”). Test scores range from 0 to 30 and scores below 24 are an indication of moderate-to-severe dementia, depending on patient age and education level. The test has good sensitivity (90%) but poor specificity (60%) for dementia because it is relatively insensitive to mild cognitive dysfunction, especially in higher-functioning patients.

## Neurologic Changes of Normal Aging

### Introduction

In order to understand dementia that usually occurs in the elderly, one must first understand the changes that occur with normal aging. In the past decade, studies have identified neurologic changes that occur in normal aging separate from those that develop from disease. Overall, there is a slow loss of many neurologic functions with normal aging, but the loss is subtle, allowing the individual to continue to function normally past age 100 years.

### COGNITION

There is an age-related decline in the (1) speed of central processing, (2) performance on timed tasks, (3) recent memory retrieval, and (4) learning. However, verbal intelligence remains well preserved at least through age 80 years. The elderly require more time to process a question centrally, although the answer usually is correct. Memory studies find that, compared with young adults, the elderly have a 10% decline in the time of their immediate recall from working memory. In “benign senescent forgetfulness,” the elderly often describe increased forgetfulness and vague recollections, but studies suggest that this is more from decreased new learning than actual forgetfulness. New learning in the elderly continues throughout life, but the period of time the elderly can concen-

trate diminishes. Some aspects of cognition remain quite stable in the elderly, such as recognition memory and tasks involving well-learned knowledge. While the actual IQ score does not decrease with age because it is corrected for age, the raw score necessary to obtain an IQ of 100 decreases for performance IQ, but not verbal IQ.

#### VISION AND HEARING

The cranial nerves most affected by aging are those for vision and hearing. Visual loss diminishes due to (1) the pupils becoming progressively smaller and less reactive to light and accommodation, (2) increasing opacity of the lens and vitreous, and (3) subtle retinal changes. Thus presbyopia occurs, with the admittance of less light that is poorly focused on an impaired retina. The range of vertical eye movements diminishes with advanced aging.

Presbycusis is a progressive elevation of the auditory threshold, especially for higher frequencies. Changes of aging, more prominent in men than women, often include loss of cochlear hair cells, degeneration of spiral ganglion neurons, and atrophy of the cochlear stria vascularis. The normal speech range is from 500 to 3000 Hz. When cochlear damage progresses to impair these frequencies, functional hearing loss develops.

#### STRENGTH, GAIT, AND COORDINATION

With normal aging there is a progressive decline in muscle bulk and strength, speed, and coordination of movement. Muscle wasting is most noticeable in intrinsic hand muscle. Grip strength declines in 85% of normal individuals over age 60, which is out of proportion to loss of muscle bulk. Activities of daily living require 1/3 more time in the elderly, and there is less precise coordination. However, finger-to-nose testing remains normal. Changes of gait in advancing age include a wider-based walking stance, shorter steps, mild loss of accompanying arm swing, and slightly stooped posture.

#### SENSATION

The elderly have a mild progressive loss of vibration and position sense, mainly in the feet, from a progressive loss of distal peripheral nerve sensory nerve axons. The result is poorer balance, especially with the eyes closed. There is an accompanying diminishment of the ankle jerk, but not loss of it.

Pathologic reflexes, such as clonus, Babinski signs, or grasp reflexes, are not normal aging phenomena.

## Dementia

Dementia is an acquired loss of intellect (IQ) that is sufficient to impair the individual's reasoning, planning, and problem-solving skills, as well as the ability to think abstractly, comprehend complex ideas, learn quickly, and learn from experience. Dementia is the fourth most-common cause of death in the United States. The exact prevalence is unknown, but 4 million Americans have dementia and another 3 million have mild cognitive impairment. In most patients, the dementia is progressive (as in Alzheimer's disease), but can be static (as from hypoxia due to cardiac arrest). Unfortunately, the vast majority of causes are not reversible.

There is no single pathophysiologic mechanism that produces all types of dementia, but the final common pathway is loss of neurons in one or more of the multimodal association cortex regions (prefrontal cortex, limbic system, and parietal lobe). The neuronal loss can occur abruptly by (1) loss of cerebral arterial blood flow from cardiac arrest, (2) cerebral arterial occlusion from thrombosis or emboli, (3) loss of critical brain nutrients from hypoxemia or hypoglycemia, (4) neuronal toxins, (5) head trauma, and (6) CNS infections. Progressive neuronal loss results from (1) neurodegenerative disease, (2) chronic exposure to neurotoxins, (3) vitamin deficiencies, (4) CNS infections, (5) accumulation of cerebral infarctions, and (6) chronic systemic or metabolic encephalopathies (Table 11-3).

Not all patients experience similar clinical deficits. Most patients develop loss of IQ along with additional problems of higher cortical function. For example, patients often forget easily, have difficulty learning new information, and express subtle aphasias and apraxias. Table 11-4 lists the major tests that should be obtained in patients with dementia. In the early stages of dementia, objective neuropsychologic testing (especially memory tests) is abnormal. As the dementia progresses, cerebral atrophy especially is commonly seen on neuroimaging. These images may demonstrate additional abnormalities depending on the disease.

**Table 11-3 Major Causes of Dementia in the United States**

<b>Neurodegenerative and Neurogenetic Diseases*</b>
<p><b>Alzheimer's disease</b> (60%)</p> <p><b>Alzheimer's disease plus other causes</b> (especially multiinfarct dementia) (15%)</p> <p><b>Dementia with Lewy bodies</b> (10%)</p> <p>Down's syndrome</p> <p>Tauopathies (such as progressive supranuclear palsy and corticobasal degeneration)</p> <p>Huntington's disease</p> <p><i>Hepatolenticular degeneration (Wilson's disease)†</i></p>
<b>Cerebrovascular Disease</b>
<p>Multiinfarct dementia</p> <p>Subacute arteriosclerotic encephalopathy (Binswanger's disease)</p> <p><i>Central nervous system vasculitis</i></p>
<b>Infectious Disease</b>
<p>Creutzfeldt–Jakob disease</p> <p>Sequelae of viral encephalitis (such as herpes simplex encephalitis)</p> <p><i>Neurosyphilis</i></p> <p><i>Human immunodeficiency virus infection (acquired immunodeficiency syndrome dementia)</i></p>
<b>Systemic Metabolic Encephalopathies</b>
<p><i>Hypothyroidism</i></p> <p><i>Hepatic encephalopathy</i></p> <p><i>Vitamin deficiencies (B<sub>1</sub> and B<sub>12</sub>)</i></p> <p><i>Hypoxic disorders</i> (such as cardiac arrest and chronic obstructive pulmonary disease)</p>
<b>Toxic Encephalopathies</b>
<p><i>Heavy metals</i> (such as lead, arsenic, and mercury)</p> <p><b>Alcoholism</b></p> <p>Carbon monoxide</p>
<b>Immune Disorders</b>
<p><i>Systemic lupus erythematosus</i></p> <p>Paraneoplastic syndromes</p>
<b>Psychiatric disorders</b>
<p><i>Depression</i></p>

\* **Bold** type represents common causes, with "( )" being their approximate incidence.

† Type in italics represents causes that may be reversible.

*Mild cognitive impairment* (MCI) is the term used to describe the earliest signs and symptoms of a dementia. This is the transitional zone between normal aging and dementia. These individuals complain of memory impairment but still lead relatively independent lives. MCI is defined as occurring in patients who have adequate general cognitive functioning and perform normally in activities of daily living but show subjective memory impairment that is corroborated by a spouse or friend and have objective memory impairment on standardized memory tests that is at least 1.5 SD below the normal for age and education status. Long-term studies of individuals with MCI find 12% per year develop frank dementia compared with 1% for age-matched controls. Limited autopsy studies find that 90% of patients who progress to dementia have Alzheimer's disease.

## Alzheimer's Disease

### Introduction

Alzheimer's disease (AD) accounts for 60% of dementia in the elderly. Of the elderly, 4 million currently suffer from this disease, and the prevalence is expected to climb to 14 million by 2050. About 1,000 elderly adults are diagnosed daily with AD. The prevalence rate is 1% for individuals ages 60 to 64 years and doubles every 5 years to reach 40% by the age of 85 years.

### Pathophysiology

The hallmark pathology of AD is an excess of neuritic plaques and neurofibrillary tangles in the cerebral cortex compared with healthy age-matched controls. Neuritic plaques consist of a central core of  $\beta$ -amyloid protein surrounded by a ring of astrocytes, microglia, and dystrophic neurites. The dystrophic neurites often contain abnormal paired helical filaments. Neurofibrillary tangles are abnormal accumulations in the neuronal cell body and dendrites of paired helical filaments of abnormally hyperphosphorylated tau proteins that can be seen by electron microscopy or by light microscopy after silver staining. Neuritic plaques and neurofibrillary tangles are maximally seen in the hippocampus, limbic system, and frontal lobes (Figure 11-5).

**Table 11-4 Laboratory Workup of Patient with Dementia**

<b>Blood Tests</b>
Hemogram
Electrolytes
Glucose
Calcium
Creatinine
Liver function studies
Thyroid-stimulating hormone
Syphilis serology (rapid plasma reagin) [RPR] test and fluorescent treponemal antibody absorption test (FTA-ABS) if RPR is positive)
Vitamin B <sub>12</sub> level
Special tests (such as ceruloplasm level for suspected Wilson's disease)
<b>Neuroimaging</b>
Magnetic resonance imaging to evaluate for central nervous system (CNS) masses, hydrocephalus, multiple infarctions, and infection)
Computed tomography if patient is poorly cooperative
<b>Neuropsychologic Tests</b>
These tests provide a precise quantitation of various cognitive functions. Tests are available to evaluate IQ, memory, apraxias, aphasias, and behavior. They are indicated for (1) diagnosing whether dementia is present, (2) characterizing the cognitive deficits of an atypical dementia, (3) determining whether the dementia is static or progressive, and (4) following response to treatment.
<b>Lumbar Puncture with Cerebrospinal Fluid (CSF) Exam</b>
CSF exam is indicated for patients with cancer, CNS infection, systemic infection, reactive syphilis serology, immunosuppression, vasculitis, rapidly progressive course, atypical course, or age younger than 60 years.
Cell count
Glucose level
Total protein and immunoglobulin G levels
Oligoclonal bands
Bacterial and fungal cultures
Venereal Disease Research Laboratory slide test-CSF (CSF-VDRL)
<b>Optional tests based on clinical presentation and family history</b>
Genetic tests (such as for Huntington's disease)
Urinary heavy metals (such as for lead, mercury, or arsenic)
Toxicology screen (for recreational drugs and medications containing anticholinergics, bromine, sedatives, barbiturates, or tranquilizers)
Serological tests (such as for human immunodeficiency virus)
Antinuclear antibodies
Electroencephalogram
Single photon/positron emission computed tomography imaging studies

Additional histological features of AD include the loss of cortical neurons, producing cerebral atrophy with enlarged ventricles (hydrocephalus ex vacuo), marked reductions in the density of

cortical synapses, and granulovascular degeneration in hippocampal neurons. Neuronal loss in the nucleus basalis accounts for the loss of cholinergic neurons and their cortical axons.

The pathogenic mechanisms that produce these histologic changes are incompletely understood. Current evidence points to the accumulation of an abnormal amyloid protein as being central to the cerebral damage. The  $\beta$ -amyloid gene encodes a large protein, amyloid precursor protein, which is normally inserted into neuronal membranes with a  $\beta$ -amyloid fragment of 40 to 42 amino acids located outside the cell. In AD the  $\beta$ -amyloid fragment is abnormally cleaved, producing a  $\beta$ -amyloid peptide that is poorly catabolized, accumulates locally, and is toxic to neurons.

The most potent risk factor for developing AD is the presence of the apolipoprotein (apo) E4 allele. Of the three forms, E2, E3, and E4, only E4 increases the likelihood of AD. The lifetime risk for individuals carrying an E4 allele is 29% compared with 9% for individuals carrying the other alleles. How the E4 protein increases the risk is unclear. Other risk factors for developing AD are increasing age, head trauma, low folate and vitamin B<sub>12</sub> levels, and elevated homocysteine levels. Some risk factors such as fewer years of formal education, low income, and lower occupational status appear to work by decreasing the amount of “cognitive reserve” the patient can lose before dementia becomes evident.

### Major Clinical Features

Table 11-5 lists common early and late clinical features of AD. Patients usually are apathetic and have impairment of recent memory and some preservation of remote recall memory. Patients lose the ability to perform previously learned complex tasks such as balancing a checkbook, handling money, and reading street maps. They also lose the ability to reason, plan activities, hold complex conversations, and play games such as bridge or chess. Except in the very early stage, patients lose insight into their cognitive problems and deny or ignore their presence. Thus patients may get lost driving their car or walking about in their own town. Some patients experience unexpected periods of agitation, anger, and abnormal sexual activity. As the disease progresses, apraxias become more evident with the inability to dress, prepare a meal, or groom. Meals are often forgotten and patients may become malnourished. Surprisingly, language function is maintained until late, so patients often can carry out simple “cocktail party” conversations

**Table 11-5 Common Features of Alzheimer’s Disease**

Early Disease	Later Disease
Progressive decline in recent memory	Loss of insight
Progressive decline in executive functioning	Loss of judgment
Normal speech and gait	Behavioral changes with marked mood swings and depression
Mild to moderate frontal-temporal brain atrophy on neuroimaging	Global dementia including apraxias and severe memory loss
Normal Cerebrospinal fluid	Terminal apathy and withdrawal from social situations, leading to virtual mutism  Marked brain atrophy on neuroimaging with hydrocephalus ex vacuo

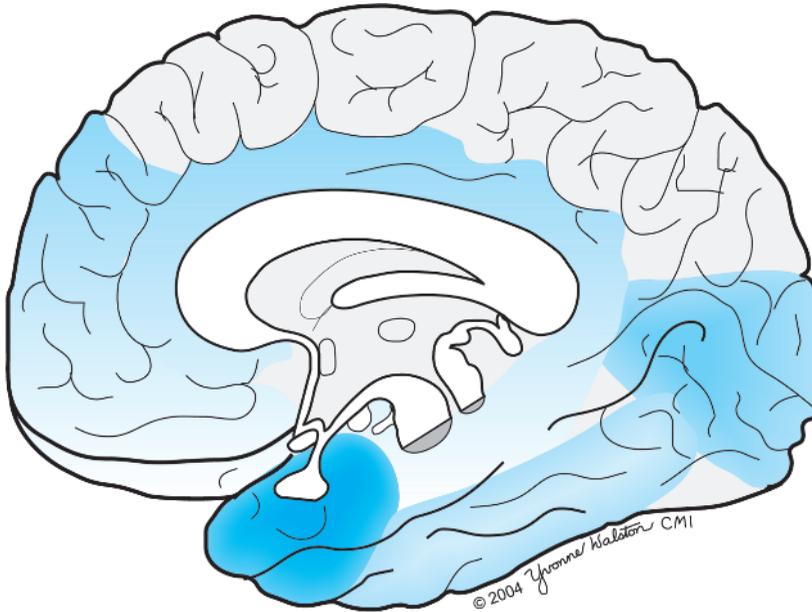
yet cannot discuss current events. As the disease progresses, patients lose the ability to recognize close friends, carry out meaningful conversations, and keep track of time and place.

Nearly 10% of AD occurs in association with vascular dementia. Vascular dementia is characterized pathologically by widespread white matter changes presumably from ischemic brain injury, and multiple infarcts. Clinically, vascular dementia is identified by a tendency for a stepwise progression of dementia.

The clinical or presumptive diagnosis of AD is based on an insidiously progressive decline in intellect, especially recent memory and executive functioning, beginning after age 50 years. This progresses over several years to a global dementia, including loss of insight and judgment as well as behavioral changes. No other medical causes of dementia should be present.

### Major Laboratory Findings

No laboratory test establishes the diagnosis of AD. A definite diagnosis is based on characteristic neuritic plaques and neurofibrillary tangles seen on brain biopsy or autopsy. Routine blood and CSF tests are normal. Neuroimaging usually demon-



**Figure 11-5** Schematic brain of patient with Alzheimer's disease showing locations of neuritic plaques and neurofibrillary tangles.

strates symmetrical brain atrophy that is out of proportion for age, with an accompanying hydrocephalous ex vacuo of the third and lateral ventricles. An EEG shows a diffuse slowing of background activity that is nonspecific. PET/SPECT scans demonstrate hypometabolism and reduced blood flow to the temporal and parietal lobes.

### Principles of Management and Prognosis

There is no method to stop or reverse the progression of AD. However, cholinesterase inhibitors produce modest transient improvements in memory and cognition and may reduce behavioral outbursts. Low doses of psychoactive medications may be required to treat patients who have frequent outbursts of anger or agitation. Studies are underway to determine if reducing amyloid production and aggregation or enhancing amyloid removal may offer clinical benefit.

The heart of management lies in a quality caregiver. Family caregivers provide most of the daily care, which can be a 24-hour-a-day undertaking since patients require almost constant supervision. Ideally, patients should be able to safely wander without becoming lost, have meals provided and supervised, and have domestic needs done by oth-

ers (shopping, bill paying, and keeping doctor's appointments). Sudden worsening of confusion occurs when the patient is moved to new surroundings such as a hospital or nursing home. The family caregiver is at risk of becoming exhausted, depressed, and feeling guilty as the disease relentlessly worsens. Use of other family members or professional attendants to allow caregivers time for themselves, or even brief respites where the patient is placed in a nursing home setting, may be needed. It is strongly recommended that the spouse have scheduled time away and respite care.

The duration of AD, once diagnosed, is about 3 to 5 years and death usually comes from pneumonia and other systemic illnesses.

### Mental Retardation

Mental retardation is a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. The disability usually begins in early life and before age 18. This definition must be considered within the context of community environments typical of the individual's age peers and culture as

**Table 11-6 Major Risk Factors for Mental Retardation**

Time Period	Biomedical	Social	Behavioral	Educational
<b>Prenatal</b>	Chromosomal disorders Single-gene disorders Metabolic disorders Cerebral dysgenesis Maternal age and illness	Maternal malnutrition No access to prenatal care	Maternal drug use Maternal alcohol use	Parental cognitive disability without supports
<b>Perinatal</b>	Prematurity Birth injury Neonatal disorders	Lack of access to birth care	Parental rejection of child or caretaking	Lack of medical services
<b>Postnatal</b>	Traumatic brain injury Malnutrition Meningitis Degenerative disorders	Impaired child caregiver Lack of infant stimulation Placement in institution	Child abuse Inadequate safety measures Social deprivation	Delay in medical care or diagnosis Inadequate education services Impaired parenting

well as disabilities in communication, sensorimotor function, and behavior. Disability is the expression of limitations in individual function in a social context and represents a substantial disadvantage to the individual.

Limitation in adaptive behavior affects both daily life and the ability to respond to life changes and environmental demands. Examples of conceptual adaptive skills include language, reading, money concepts, and self-direction. Examples of social adaptive skills include interpersonal conduct, responsibility, self-esteem, gullibility, naiveté, and following rules and laws. Examples of practical adaptive skills include activities of daily living (eating, dressing, and toileting), functional aspects of daily life (transportation, housekeeping, money management, and taking medication) and occupational skills.

Mental retardation is often classified with respect to severity. Mental retardation that is mild presents with an IQ between 50 and 70; moderate is between 35 and 49, severe between 20 and 34, and profound below 20.

Mental retardation may occur from a wide variety of biomedical, social, behavioral, and education problems that occur in the prenatal, perinatal, or postnatal periods. Table 11-6 lists risk factors for each time period. Table 11-7 lists the major causes of mental retardation. It is important to understand that some causes of mental retardation are due to progressive degenerative illnesses resulting in steady worsening of the IQ and mental retardation. Other causes are static (such as peri-

natal birth injury) and do not progress as the child grows. However, the manifestations of the mental retardation may evolve as the child fails to gain expected childhood developmental skills. Appro-

**Table 11-7 Common Causes of Mental Retardation**

<b>Prenatal</b>
Fetal alcohol syndrome
Down's syndrome
Fragile-X syndrome
Cerebral dysgenesis
Autism (not all cases)
<b>Perinatal</b>
Birth injury
Marked prematurity and very low birth weight, especially with periventricular hemorrhage
Infant illnesses such as severe sepsis, bacterial meningitis, and undiagnosed hypothyroidism
<b>Postnatal</b>
Head trauma from child abuse (shaken baby syndrome), sports injury, or automobile accident
Severe malnutrition such as marasmus or kwashiorkor
Toxic metabolic disorders such as lead intoxication
Severe epilepsy
Childhood degenerative diseases
Infections such as bacterial meningitis, whooping cough, and encephalitis

priate treatment of the child with mental retardation requires establishing the etiology and treating the cause, if possible, as well as maximizing the personal support the child requires. Mental retardation is often accompanied by physical disabilities that also require skilled attention. In children with static mental retardation the IQ may not improve over time, but the function in adaptive skills can and this would be significant in the individual's quality of life.

## RECOMMENDED READING

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Albert ML, Knoefel JE, eds. *Clinical Neurology of Aging*. New York: Oxford University Press; 1994. (Covers many neurologic aspects of normal aging.)

Cummings JL, Cole G. Alzheimer's disease. *JAMA* 2002;287:2335–2338. (Current review of pathophysiology and treatment.)

Luckasson R, Borthwick-Duffy S, Buntinx WHE, et al. *Mental Retardation: Definition, Classification, and Systems of Support*, 10th ed. Washington DC: American Association of Mental Retardation; 2002. (Current overview of mental retardation and available support systems.)

Petersen RC. Aging, mild cognitive impairment, and Alzheimer's disease. *Neurol Clin* 2000;18:789–805. (Nice review of mild cognitive impairment and the workup of patients with suspected dementia.)

# 12 DISORDERS OF THE EXTRAPYRAMIDAL SYSTEM

## Overview

The pyramidal system is the motor/premotor cortex and corticospinal tract that governs voluntary movements. The extrapyramidal system refers to several systems whose neurons are largely located in the basal ganglia that oversee nonvoluntary, competing aspects of the motor system. Thus one can conceptualize the basal ganglia and substantia nigra as being organized to facilitate voluntary movements and to inhibit competing movements that interfere with the desired movement. This is accomplished by enabling the brain to produce the desired motor pattern while creating a surround inhibition of competing motor movements (Figure 12-1). Constant loss of surround inhibition would result in hypokinetic movements while intermittent or fluctuating changes of surround inhibition could result in abnormal hyperkinetic movements.

Extrapyramidal disorders refer to movement disorders that result from damage or presumed dysfunction of the basal ganglia and their brainstem and cerebellar connections. Movement disorders are characterized by either excessive (hyperkinetic) or reduced (bradykinetic) activity. Parkinson's disease is the classic hypokinetic

movement disorder while diseases that express chorea, tremor, myoclonus, and tics represent hyperkinetic movement disorders. Below are common types of dyskinesias seen in many patients.

## Chorea

Choreas are sudden, brief, nonrepetitive, nonperiodic, involuntary jerking movements involving shifting muscles or muscle groups of the arms, hands, legs, tongue, or trunk that cannot be voluntarily suppressed.

## Dystonia

Dystonias are strong, sustained, and slow contractions of muscle groups that cause twisting of a limb or the entire body. The contractions are often painful and may appear disfiguring. The dystonia lasts many seconds to minutes and occasionally hours, producing a dystonic posture.

## Athetosis

Athetosis consists of sinuous, writhing, alternating contractions of the arms or legs that can blend with dystonia and chorea.



**Table 12-1 Tremor Type by Clinical Presentation**

<b>Tremor Type (Other Common Names)</b>	<b>Characteristics (Examples)</b>
<i>Rest Tremor</i>	Present involuntarily at rest when body part is supported against gravity and muscles are not purposefully contracting (Parkinson's disease tremor)
<i>Action Tremor (Postural Tremor, Static Tremor)</i>	Present when voluntarily maintaining a limb still against gravity, such as holding arms outstretched. Usually bilateral but may be asymmetric Low-to-medium amplitude and medium-to-high frequency Present during some voluntary movements such as writing or pouring, but does not interfere with general coordination (essential tremor, physiologic tremor)
<i>Intention Tremor (Kinetic Tremor, Cerebellar Tremor)</i>	Present during voluntary movement and often perpendicular to direction of movement Medium amplitude and low frequency Often amplifies when limb approaches the target Interferes with coordination (cerebellar-type tremor as seen in finger-to-nose movements)

ing that multiple etiologies may account for essential tremor. At present, the actual pathophysiology of how sporadic or genetic cases develop the tremor is unknown, as structural lesions have not been recognized. PET studies have shown increased blood-flow activity in the cerebellum, red nucleus, and inferior olivary nucleus, implying that the oscillatory circuitry involves those nuclei. There is debate as to whether essential tremor represents a pathologic exaggeration of a normal physiologic tremor.

### Major Clinical Features

The characteristic history is one of slowly progressive or stable bilateral tremors of the hands that began about age 45 years. The tremor is of medium to high frequency, of fine amplitude, sustained, present immediately with arms outstretched (action tremor), and absent at rest. The tremor seldom interferes with activities of daily living, but patients often complain of problems in writing or spilling when drinking their coffee. Occasionally the tremor also may involve the head, legs, or voice. Patients relate that the tremor worsens with anxiety, coffee, and some medications but diminishes when drinking alcohol. Weakness, sensory loss, or changes in deep tendon reflexes do not occur with the tremor. Patients should not have features of Parkinson's disease.

Several drugs that may worsen essential tremor or exaggerate a physiologic tremor include lithium, levothyroxine,  $\beta$ -adrenergic bronchodilators, valproate, prednisone, caffeine, and selective serotonin-reuptake inhibitors (SSRIs).

### Major Laboratory Findings

No laboratory test is diagnostic; diagnosis rests on the history and exam. Routine blood tests are normal and neuroimaging of the spinal cord and brain are normal.

### Principles of Management and Prognosis

Patients with mild symptoms usually do not require treatment once they are reassured that they do not have Parkinson's disease and that the tremor rarely becomes incapacitating. Many patients find that a small amount of alcohol (glass of wine or beer) suppresses the tremor for hours and is useful when entertaining friends. For patients with severe essential tremor or whose occupation is impaired by the tremor, propranolol and primidone have been successful in reducing the tremor severity. In rare cases of severe tremor, surgical implantation of electrical stimulators in the thalamus or stereotactic thalamotomy may be indicated.

## Parkinson's disease

### Introduction

Parkinson's disease affects more than 1 million Americans and has a prevalence rate of 1% in individuals over age 55 years. The direct annual cost in the United States is over \$10 million. Both sexes are equally involved, and the incidence climbs exponentially with increasing age to 7% above age 70 years. Idiopathic Parkinson's disease usually begins above age 55, while patients with genetic causes of Parkinson's disease starting as early as age 30 to 45 years. Parkinson's disease has a dramatic impact on quality of life and produces a marked reduction in life expectancy.

The hallmarks of Parkinson's disease and parkinsonism are bradykinesia (diminished speed and spontaneity of voluntary movements), resting tremor, cogwheel rigidity, gait changes, and late postural instability, all due to reduced levels of dopaminergic transmission from structural or functional disruption of nigrostriatal pathways. Parkinson's disease refers to the primary idiopathic form and represents 2/3 of all parkinsonism. Parkinsonism is the secondary form and refers to the above clinical and biochemical features that develop from specific causes such as repeated head trauma (boxing), infections of the upper midbrain, medications that affect dopamine transmission, or CNS diseases that damage the nigrostriatal pathway and other brain areas.

### Pathophysiology

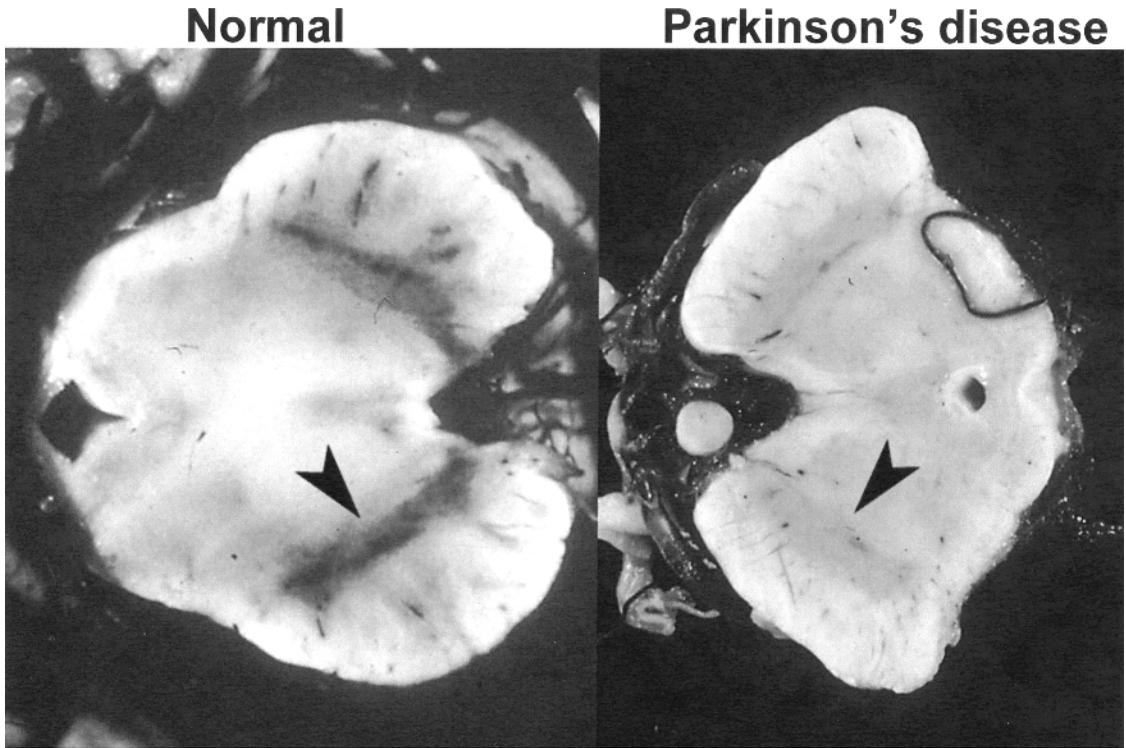
Idiopathic Parkinson's disease results from the slowly progressive death of CNS dopaminergic neurons and some adrenergic and serotonergic neurons. Death of the melanin-containing pigmented dopaminergic neurons in the pars compacta of the substantia nigra is responsible for the motor signs of this disease. Evidence suggests that the death of dopaminergic neurons begins a decade before symptom onset. When the neuronal loss reaches about 70% of total neurons, symptoms begin. The cause of dopaminergic neuronal death is unknown, but current theories include exposure to environment neurotoxins, abnormal mitochondrial function, abnormal oxidative metabolism, and generation of misfolded  $\alpha$ -synuclein protein, which is toxic.

Grossly, there is loss of pigmentation in the substantia nigra and other dopaminergic nuclei such as the locus ceruleus (Figure 12-2). Microscopically, there is loss of small pigmented neurons in the substantia nigra and eosinophilic, cytoplasmic inclusion bodies surrounded by a clear halo (Lewy bodies) in remaining neurons, which contain aggregations of neurofilaments and  $\alpha$ -synuclein protein attached to ubiquitin.

Substantia nigra dopaminergic neurons project to the ipsilateral striatum (caudate nucleus and putamen). Dopamine release from substantia nigra neurons stimulates D1 receptors and inhibits D2 receptors, resulting in the striatum sending impulses to the motor cortex (called the basal ganglia–thalamocortical motor circuit) in a direct excitatory pathway via thalamic nuclei. Concomitant inhibitory impulses to the motor cortex in a polysynaptic indirect pathway via globus pallidus externa, subthalamic nucleus, and thalamic nuclei are also sent. Loss of dopaminergic nigral cells leads to striatal dopamine depletion and overall decreased motor cortex excitation. The loss of excitatory stimulation decreases excitatory activity of the direct pathway to the motor cortex and increases inhibitory activity of the indirect pathway to the motor cortex. Not yet completely understood, the increased inhibitory input to the motor cortex causes bradykinesia.

Using the surround inhibition model of the basal ganglia, the loss of substantia nigra input to the striatum would cause loss of inhibition of competing motor movements (Figure 12-1). For example, when a normal individual flexes an arm, the bicep fires (desired movement) and the tricep is inhibited (surround inhibition). In the patient with Parkinson's disease, flexion of the arm fires both the bicep (desired movement) and tricep (loss of surround inhibition), resulting in bradykinesia. The tremor of Parkinson's disease is felt to be secondary to interruption of the CNS oscillatory pathway in the globus pallidus and thalamus.

Five percent of Parkinson's disease is due to autosomal dominant mutation in the *parkin* gene and occasionally in the  *$\alpha$ -synuclein* gene. The role of  $\alpha$ -synuclein in the pathogenesis of Parkinson's disease is receiving attention since  $\alpha$ -synuclein is normally abundant in neurons and presynaptic terminals, as well as in Lewy bodies. The *parkin* gene product appears to be involved in identifying



**Figure 12-2** Gross brain specimen in patient with Parkinson's disease, showing loss of pigmentation in the substantia nigra (arrows) and locus ceruleus.

proteins such as  $\alpha$ -synuclein for degradation via the ubiquitin pathway.

### Major Clinical Features

The diagnosis of Parkinson's disease is usually made by the presence of asymmetrical bradykinesia, cogwheel rigidity, resting tremor, and good response to levodopa. Rigidity consists of a constant resistance to passive muscle stretching in both flexors and extensors throughout range of motion due to stretching force induction of some antagonistic motor units to fire. In Parkinson's disease, rapid flexion and extension or rotation of the wrist or elbow often elicits a ratchetlike feeling (cogwheel rigidity).

Table 12-2 lists the common clinical features of Parkinson's disease in the early, middle, and advanced stages. The disabling feature is bradykinesia. One patient described early bradykinesia as walking in a swimming pool with water up to the neck and advanced bradykinesia as walking in a swimming pool filled with molasses. Thus,

patients spend enormous amounts of energy performing routine activities of daily living.

In a simplistic fashion, everything "slows down" in the patient with Parkinson's disease. Limb and chewing movements are slow; gait is slow, shuffling, difficult to initiate, and often with a stooped posture; standing balance is impaired from slow corrective steps to maintain balance, so falling is common; spontaneous facial expression is minimal (masked facies); gut peristalsis is slow so constipation is common; and mental activities are slower than normal so there are both less spontaneous speech and delayed answers to questions spoken in a soft, dysarthric voice. In 40% a dementia develops in the later disease stages.

### Major Laboratory Findings

Routine blood and CSF studies are normal. Neuroimaging is seldom helpful in diagnosing Parkinson's disease or distinguishing it from other causes of parkinsonism. In Parkinson's disease, PET studies with radioactive fluorodopa demonstrate

**Table 12-2 Clinical Features of Parkinson's disease**

Clinical Feature	Description	Disease Stage
Bradykinesia	Paucity or slowness in movements	E, I, L
Cogwheel Rigidity	Ratchet sensation upon moving elbow or wrist	E, I, L
Resting Tremor	"Pill-rolling" tremor of hands; often asymmetrical	E, I, L
Masked Facies	Diminished spontaneous facial expressions	E, I, L
Gait Difficulties	Start hesitancy, shuffling short steps, stooped posture, and trouble stopping and turning	I, L
Hypokinetic Dysarthria	Low volume, monotone, and garbled speech without aphasia	I, L
Balance Problems	Tendency to fall while walking or standing, especially with eyes closed	I, L
Constipation	Slow peristalsis made worse from some drugs	I, L
Orthostatic Hypotension	Fall in blood pressure upon arising that causes dizziness and syncope	L
Sleep Disturbances	Insomnia, restless legs, and daytime drowsiness	I, L
Cognitive Disorders	Hallucinations, depression, and dementia in 40%	I, L
Decreased Arm Swing	Lack of associated arm swing on walking; often asymmetrical	E, I, L

\* Stages: E = early (1 to 5 years after diagnosis), I = intermediate (5 to 10 years), L = late (>10 years)

reduced uptake greater in the putamen than in the caudate.

### Principles of Management and Prognosis

Since no treatments can halt disease progression of Parkinson's disease, management aims at minimizing the symptoms and maximizing patient functioning and safety. Presently there is controversy whether drugs such as monoamine oxidase inhibitors (e.g., selegiline) can slow the rate of early disease progression.

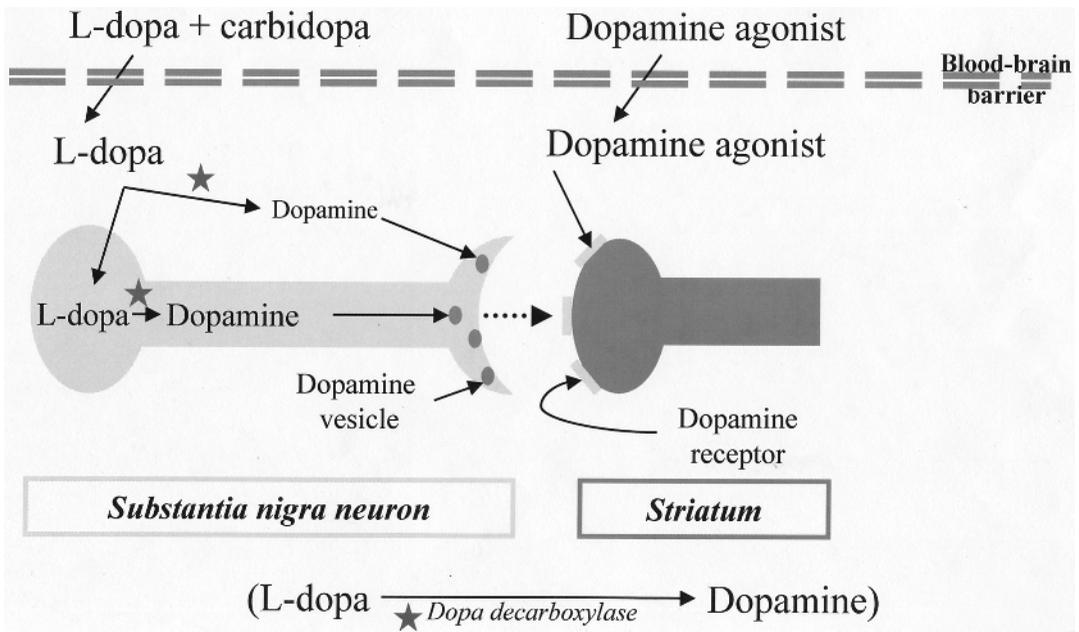
The mainstay of early treatment is providing additional dopamine or dopamine agonists to the striatum. Dopamine cannot cross the blood-brain barrier and causes considerable systemic nausea and hypotension by stimulating peripheral dopamine pathways. Levodopa was found to cross the blood-brain barrier and to be converted in the brain to dopamine by the enzyme dopa-decarboxylase. To minimize systemic conversion of levodopa to dopamine, the DOPA-decarboxylase inhibitor carbidopa is added to levodopa. Carbidopa does not cross the blood-brain barrier, so CNS conversion of levodopa is unaffected. Levodopa is converted to dopamine within the dopamine neuron cell body and transported via axoplasmic flow to the nerve terminal. Levodopa is also converted to

dopamine at the distant presynaptic nerve terminal, where it is taken up and stored by the nerve terminal. Dopamine agonists, such as bromocriptine and pramipexole, cross the blood-brain barrier to act directly upon D1 or D2 postsynaptic terminals in the striatum (Figure 12-3).

Levodopa is the most potent of all drugs and is particularly helpful in reducing bradykinesia. Controversy exists as to whether its early usage may accelerate the time to developing levodopa complications, but the weight of evidence suggests the neurotoxic effect is minimal, if any.

In early Parkinson's disease, complete relief of the bradykinesia is achieved with levodopa and carbidopa in low doses three times a day (tid) or from a slow release formulation given once (qd) to twice (bid) daily. Anticholinergic drugs may help the tremor but have considerable side effects in the elderly, including constipation, urinary retention, confusion, memory loss, and hallucinations.

After 5 years' duration, it becomes increasingly difficult to achieve and maintain ideal CNS levels of dopamine. Patients often develop dyskinesias or "on" phenomena 1 to 2 hours after taking levodopa medication; this is felt to represent excessively elevated CNS drug levels, which stimulate nonessential dopamine pathways. Patients experience involuntary movements of their arms, legs, and



**Figure 12-3** Dopaminergic therapy for Parkinson's disease.

face in an irregular fashion during a time when their bradykinesia is minimal. The levodopa level then rapidly falls below optimal CNS levels, producing freezing spells or “off” periods where the patient can hardly move. It is felt that “on-off” phenomena represent disease-related loss of dopamine buffering capacity and storage capacity by striatal dopamine nerve terminals. It is common for patients to experience hallucinations that are often visual, occur in the evening, and may or may not be frightening to the patient. About 40% of patients also develop dementia that may be from dementia with Lewy bodies or the coexistence of two common diseases of the elderly, Alzheimer's disease and Parkinson's disease. Dopamine agonists are often given to smooth out the “on-off” phenomena in the intermediate stage. Unfortunately in the advanced stage, dopamine agonists are less successful and have a similar side effect profile.

To treat the advanced stage of Parkinson's disease, experimental surgical therapies are being explored using ablation, deep-brain stimulation, or transplantation. Ablative surgery (thalamotomy, pallidotomy, and subthalamic nucleotomy) use stereotactic approaches to lesion critical basal ganglia regions in an attempt to restore more normal circuitry. Ablative therapy is irreversible, carries surgical risks, and has considerable complications

if done bilaterally. Deep-brain stimulation uses electrodes placed stereotactically in the globus pallidus interna or subthalamic nucleus to enable high-frequency stimulation of specific brain regions. Deep-brain stimulation is reversible but carries the infectious risk of long-term implantation of foreign material in the brain. Both techniques are more effective for tremor rather than bradykinesia, do not completely relieve symptoms, and require continued use of some antiparkinsonism medications. At present, the achieved response from deep-brain stimulation is similar to the best clinical improvement of the patient on an optimal dosage of levodopa but without accompanying dyskinesias.

The goal of transplantation is to replace neuronal circuitry lost by the death of substantia nigra neurons with dopamine neurons from fetal mesencephalon or adult adrenal medulla. Studies of patients receiving transplantation of fetal mesencephalon into the striatum have demonstrated survival of the dopamine neurons and even the formation of some synapses to striatal neurons. However, clinical benefit to the patient has been minimal presumably because the transplanted dopamine neurons do not spontaneously fire and release dopamine into synapses to stimulate the striatal neurons.

Education of both the patient and family about Parkinson's disease is important, as this is a slowly progressive illness. Patients should be taught to avoid sofalike seats since arising from a chair is easier; to use bars in the bathroom to minimize falls; and eventually to use walkers to improve balance while walking. A hip fracture in a patient with Parkinson's disease is serious. There is a slow recovery and a 25% mortality risk.

## Huntington's Disease

### Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterized by progressive chorea, cognitive decline, and behavioral disturbances that usually begin in mid-life. The original description came from Dr. George Huntington, a family physician, who in 1872 accurately described the clinical and genetic features of HD from his observations of three generations of illness in a family living on Long Island, New York.

HD is found around the world, with the highest prevalence (5/100,000) in populations of western European ancestry. In the United States, about 25,000 individuals have HD and another 60,000 carry the abnormal gene but are too young to express the disease. As an autosomal-dominant disorder, men and women are equally affected, and there is a high degree of penetrance in individuals who live to middle age. Women who carry the abnormal gene may give birth to affected offspring before manifesting any signs of the disease.

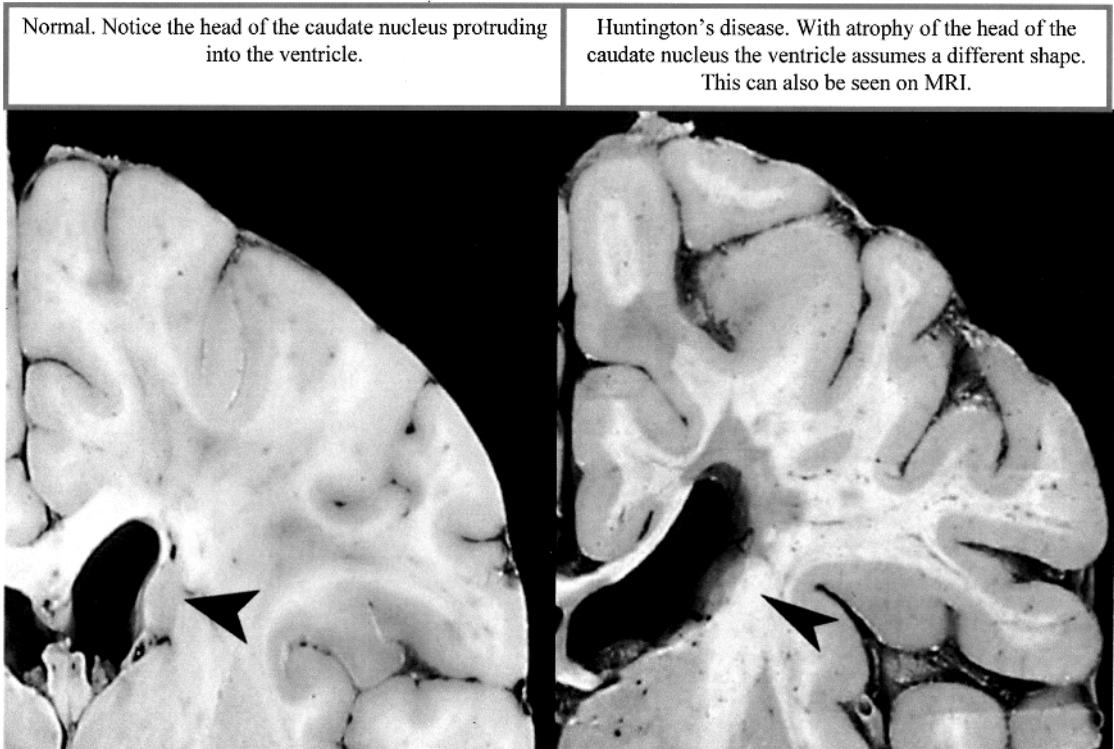
### Pathophysiology

All cases of HD develop from an abnormal extended length of CAG triplet repeats in the *HD* gene. The normal length of the trinucleotide repeats is polymorphic and ranges from 10 to 26 units, producing a string of 10 to 26 polyglutamine amino acids in the normal Huntingtin protein. The length of the CAG trinucleotide repeats is not constant, and healthy offspring normally gain or lose up to 6 repeats. However, CAG repeat lengths longer than 39 units give rise to HD. There is an inverse correlation between the length of the CAG repeats and the age of disease onset. Individuals

with repeat lengths of greater than 50 to 60 units develop juvenile HD with onset before age 20 years. Men with HD often have sperm containing an *HD* gene with many more CAG repeats than in their own somatic cell *HD* gene. Thus the next generation displays the phenomenon of increasing trinucleotide repeat length and gives rise to *anticipation*, where the disease develops at an earlier age.

Huntingtin protein is a large protein (>3,000 amino acids) that is expressed widely in neural and nonneural tissues and whose normal function is currently unknown. The amino acid sequence is not related to other proteins, but shows a high degree of evolutionary conservation. Studies in animals and man show the gene is essential in fetal development as loss of both gene copies leads to fetal death. However, fetuses containing HD protein molecules with abnormal polyglutamine length have normal fetal and childhood development. Thus current evidence suggests the pathogenesis of HD is mediated by a "gain of function" of the Huntingtin protein. In this construct, the normal Huntingtin protein functions remain intact, but a new function is detrimental to the neuron. In the end, the abnormal Huntingtin protein somehow causes premature death of selected neuronal populations.

The striking pathology in HD is atrophy of the caudate nucleus and putamen (together called the striatum). This is easily visible on gross inspection of the brain (Figure 12-4) and can be seen on neuroimaging. The neuronal cell loss is primarily from death of medium-sized spiny neurons, which account for 80% of striatal neurons. There is a relative preservation of large spiny neurons. Microscopically, intranuclear inclusions that contain fragments of Huntingtin protein are commonly seen in the striatum and there is a secondary gliosis that accompanies the neuronal loss. Medium spiny neurons are inhibitory, releasing GABA as their main neurotransmitter. Medium spiny neurons that have D2 receptors and project to the globus pallidus externa die earlier than those with D1 receptors that project to the substantia nigra and globus pallidus interna. This unequal pattern of neuronal death is thought to be responsible for adult HD patients experiencing chorea rather than parkinsonism. In juvenile HD, both neuronal populations die early, and these patients express more signs of parkinsonism. PET studies demonstrate



**Figure 12-4** Pathology of caudate atrophy in a patient with Huntington's disease.

that hypometabolism in the striatum begins prior to observable atrophy and before the onset of clinical symptoms. In addition to striatal neuronal loss, there is a moderate loss (10%–50%) of neurons in many basal ganglia nuclei and the prefrontal cerebral cortex.

### Major Clinical Features

The mean age of onset of HD is 40 years but some patients do not develop signs until past age 60 years. The clinical features are progressive disorders of movement, cognition, and behavior. Sudden nonrepetitive, nonperiodic, involuntary jerking movements involving random shifting muscles or muscle groups characterize chorea, the principle movement disorder. Chorea soon becomes very frequent during waking hours, involving the arms, hands, legs, tongue, or trunk. These movements can be voluntarily suppressed only briefly and are made worse by stress. Early in the disease, patients frequently appear fidgety and mask the involuntary limb movement by incorpo-

rating the involuntary jerk into a semipurposeful movement. Voluntary rapid eye movements from one target to another (saccadic eye movements) become slowed and uncoordinated. The inability to sustain a constant voluntary muscle contraction manifests as trouble extending their tongues for any period of time and maintaining a tight handshake (milkmaid's grip). In the early stage of the disease, patients often have normal activities of daily living and may continue to be employed. As the disease worsens, dystonia and parkinsonism appears. Dysarthria develops, with hypophonic irregular speech that becomes unintelligible. At this stage the patient depends on others for help. Dysphagia appears late and often contributes to the death of the patient.

A global decline in cognitive capabilities begins before or after the onset of chorea; only a few patients develop mild cognitive loss. The cognitive decline is characterized by loss of executive functions, with the inability to plan, sequence, and execute complex tasks; forgetfulness from loss of recent memory; slow response times; and poor

concentration. IQ score falls and dementia is present in most patients. Aphasia, apraxia, and agnosia are uncommon, but impaired visuospatial abilities develop in the late stage.

Behavioral problems often begin with personality changes manifesting as irritability, compulsivity, apathy, and anxiety that may appear years before the chorea. Depression develops in 1/3 of patients and may lead to suicide. Psychosis is uncommon (5%).

Juvenile HD has an onset of less than 20 years and is characterized by more prominent parkinsonism, especially bradykinesia. Patients have marked rigidity, severe mental deterioration, prominent motor and cerebellar signs, dysarthria, myoclonus, tics, and dysphagia. Juvenile HD progresses faster than adult HD.

### Major Laboratory Findings

Routine blood and CSF tests are unremarkable. Neuroimaging studies demonstrate atrophy of the caudate and may show atrophy of the putamen. The progressive caudate atrophy parallels loss of cognitive function and putaminal atrophy with motor decline. Neuropsychiatric tests demonstrate many abnormalities, but none are diagnostic.

The clinical diagnosis is usually made based on (1) onset in mid-life with typical chorea, cognitive loss, and behavioral changes, (2) positive family history, and (3) neuroimaging demonstrating caudate atrophy. The definite diagnosis is made by demonstrating abnormally long CAG trinucleotide repeat lengths (>40) in the *HD* gene (chromosomal locus 4p16) on genetic testing. This commercial test is useful in establishing the diagnosis in atypical cases, symptomatic individuals without a positive family history, individuals at

risk for the illness, and prenatal screening. For predictive testing to be performed, there should be (1) multidisciplinary supportive counseling before and after testing, (2) clear informed consent, and (3) confidential reporting. In general, predictive tests should not be done on minors. Although the number of CAG repeats is correlated with age of disease onset, the range of onset for each CAG length is so broad as not to be useful for individual tests and hence the length is seldom reported to the patient.

### Principles of Management and Prognosis

Since no treatment is available to cure or slow disease progression, management aims at maximizing the quality of life for as long as possible. Depression should be diagnosed early and actively treated with antidepressants. Attempts to treat the chorea seldom are beneficial to the patient. Psychosis and severe agitation can be treated with low doses of neuroleptic medications. There is no treatment for the cognitive decline.

The mean duration from diagnosis to death is 20 years, with a range of 10 to 25 years. Mean age of death is 55 years. Individuals with juvenile HD have a shorter life span.

### RECOMMENDED READING

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- Lang AE, Lozano AM. Parkinson's disease (parts 1 and 2). *N Engl J Med* 1998;339:1044–1053 and 1130–1143. (*Thorough review of clinical and pathologic issues and treatment.*)
- Louis ED. Essential tremor. *N Engl J Med* 2001;345:887–891. (*Reviews clinical features and treatment options.*)

# 13 CENTRAL NERVOUS SYSTEM INFECTIONS

## Overview

Viruses, bacteria, fungi, and parasites cause CNS infections, but bacteria and viruses are the most common agents. After entering the body via the GI tract or respiratory tract or following skin inoculation (animal or insect bite), the infectious organism sets up the initial site of replication in the GI tract, respiratory tract, or subcutaneous muscle, or vascular tissue. Most organisms reach the CNS by way of the bloodstream, but occasional organisms reach the brain via peripheral nerves or by direct entry through adjacent bone from skull fractures or infected mastoid and air sinuses.

In spite of the many infections we develop during our lifetimes, organisms rarely reach the CNS. Important protective systems include the reticuloendothelial system (which nonspecifically and efficiently removes microorganisms from the blood), cellular and humoral immune responses (which destroy specific microorganisms in the blood and at sites of infection), and the blood–brain barrier. The CNS evolved separately from other systemic organs and did not develop a sensitive immune surveillance system. The brain lacks lymphatic channels or lymph nodes. Instead, a blood–brain barrier has developed to prevent infectious organisms from entering the CNS. The

key element of the blood–brain barrier is tight junctions between endothelial cells, which prevent microorganisms or even small molecules from passing between endothelial cells to enter the brain or meninges. Endothelial cells in most of the body have gap junctions that are large enough to allow lymphocytes to pass from blood vessels into the lymphatic system. Molecules that reach the brain do so by passing through normal cerebral endothelial cells via specific transport systems that may require energy (amino acid transporters) or not require energy (glucose transporter), or because the molecule is lipid soluble. In addition, CNS endothelial cells have transporters that remove molecules, such as amino acids that are neurotransmitters, from the CNS. Larger molecules enter the CSF from blood via the choroid plexus, which acts as an ultrafilter of plasma. When intact, the blood–brain barrier not only prevents entry of infectious organisms but also maintains, under tight limits, the type and concentration of molecules free in the CNS.

However, if an infectious organism successfully enters the CNS, there are limited defenses to fight the infection. CSF has 1/1,000 the amount of antibodies and complement as blood. Since the brain lacks a lymphatic system, there are few WBCs and limited microglia (resident CNS macrophages) to

detect and combat an infection. Nevertheless, the CNS exhibits an inflammatory response, the hallmark of CNS infections. Neutrophils and mononuclear cells from blood cross areas of activated endothelial cells and open blood–brain barriers to appear in the meninges, brain parenchyma, and perivascular spaces. The lymphocytes usually show specific immune activity against the infectious agent. Unfortunately, the brain inflammatory response is ineffective against bacteria and fungi and patients usually die unless treated with appropriate antimicrobial drugs.

*The signs and symptoms of a CNS infection depend on the site of the infection and not the infectious organism. The organism determines the time course and severity of the infection.*

Table 13-1 gives the keys to suspecting a CNS infection. The patient's signs and symptoms suggest the likely location of the infection but not the infectious organism. The time course of the infection may help determine the type of infectious organism. In general, viruses produce CNS signs in hours to 1 day; aerobic bacteria in hours to a few days; anaerobic bacteria, tuberculosis, and fungi in days to weeks; and spirochetes such as *Treponema pallidum* (syphilis) in weeks to decades.

There are three major sites where infections occur in the CNS: diffusely in the meninges (meningitis), diffusely in the brain (encephalitis), and focally in the brain (abscess) (Figure 13-1). Table 13-2 lists the major signs and symptoms for infections at these sites. Although there are many different infectious organisms that can infect the meninges and brain, this chapter will discuss the

most common CNS infections that develop at these sites plus a rare infection that breaks conventional rules for infectious diseases.

## Bacterial Meningitis

### Introduction

Meningitis is due to inflammation of the meninges and is the most common CNS infection. This infection commonly is due to bacteria or viruses but can be caused by fungi, parasites, chemicals, and neoplasms. Viral meningitis occurs mainly in the spring and summer, while bacterial meningitis occurs year around. Bacterial meningitis has the highest incidence in infants, the elderly, and the immunosuppressed of any age.

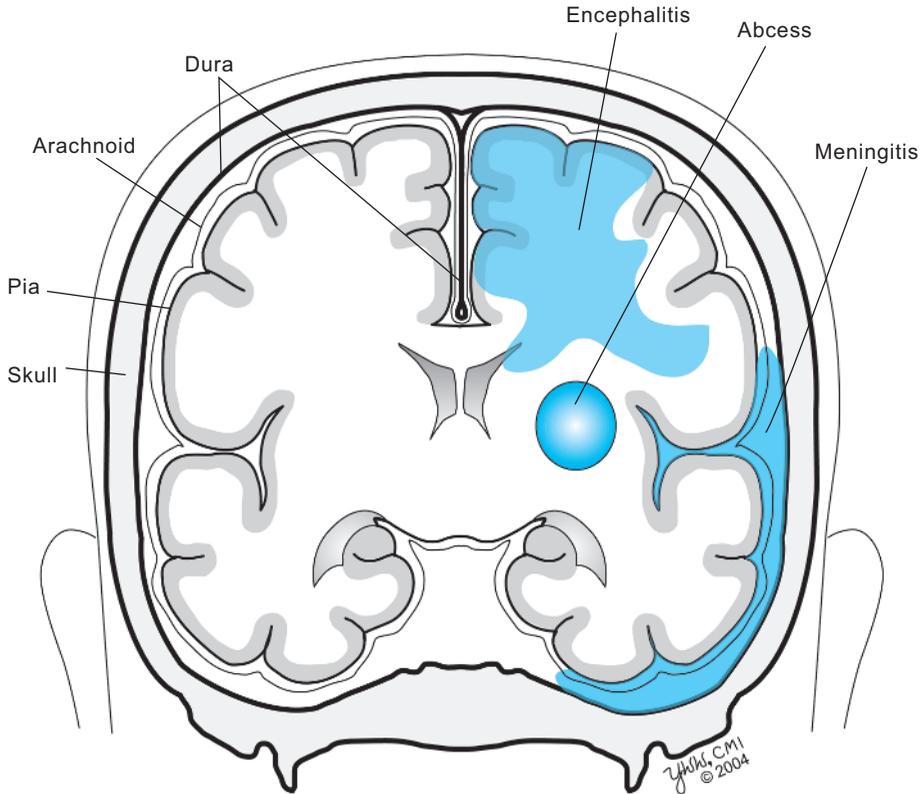
### Pathophysiology

Aerobic bacteria, both gram-positive and gram-negative, are the major causes of acute bacterial meningitis. Other bacteria such as *Borrelia burgdorferi*, *Mycobacterium tuberculosis*, and *T. pallidum* commonly cause chronic meningitis. The usual route of entry is via the upper respiratory tract, where the bacteria establish an often-asymptomatic infection. Special characteristics of the bacterial strain allow it to invade through the respiratory epithelial cells and reach capillaries, veins, and lymphatic channels. In the bloodstream the characteristics of these bacteria (such as large mucopolysaccharide coats) avoid the reticuloendothelial system, allowing them to replicate to high titers. The exact location of penetration of the blood–CSF barrier is unknown. Once within the CSF, the bacteria again replicate and release endotoxin (gram-negative bacteria) or teichoic acid (gram-positive bacteria) from their cell walls. These molecules stimulate resident macrophages and microglia to release cytokines (especially interleukin-1 [IL-1] and tumor necrosis factor [TNF]) that in turn recruit neutrophils and mononuclear cells into the CSF from the blood. In bacterial meningitis, bacteria are confined in the meninges until just before the patient's death.

As the inflammation increases, however, the brain does become irritated and damaged. Endotoxin released from the cell walls of dying bacteria and molecules released from inflammatory

**Table 13-1** Keys to Suspecting a Central Nervous System Infection

• Fever
• Acute or subacute onset
• Headache
• Focal or diffuse symptoms and signs dependent on location of infections (see Table 13-2)
• Elevated white blood cell count and erythrocyte sedimentation rate
• Increased frequency in immunosuppressed individuals



**Figure 13-1** Major sites of infection in the CNS.

cells (such as TNF and neutrophil granule molecules) can pass through the pial lining of the brain to invade and kill neurons located in the surface of the cerebral cortex and cerebellum. In addition, the meningeal inflammation can cause vasospasm or thrombosis of arteries and veins

passing in the meninges to reach the brain. Occlusion of these vessels leads to cerebral infarctions of the corresponding vascular territory. Thus while bacteria do not invade the brain, severe brain damage can result from intense meningitis.

**Table 13-2** Clinical Features of Major Central Nervous System Infections

	<b>Meningitis</b>	<b>Brain Abscess</b>	<b>Encephalitis</b>
Common	Fever Headache Stiff neck Confusion	Headache Mental status changes: confusion, stupor, and coma Seizures: generalized or focal CN VI palsy Hemiparesis Papilledema	Fever Headaches, nausea, and vomiting Mental status changes: confusion, delirium, stupor, or coma Seizures: generalized or focal Hyperreflexia, Babinski signs, or spasticity Mild stiff neck
Less Common	Seizures Stupor or coma Papilledema	Stiff neck	Tremors and dystonia Papilledema

**Major Clinical Features**

The clinical hallmark of any meningitis is fever, headache, stiff neck, and a relatively preserved mental status (Table 13-2). The headache comes from inflammation, irritating pain fibers along the base of the brain and second and third spinal nerves. The fever may be due to direct irritation of the hypothalamus or CSF IL-1 released into the CSF by the inflammatory cells. Patients with bacterial meningitis seldom present with focal neurologic signs, but hemiparesis, aphasia, ataxia, and visual loss may develop later in the clinical course. Papilledema is rarely present at onset. Patients with bacterial meningitis develop these symptoms and signs within hours to 1 day.

**Major Laboratory Findings**

The definite diagnosis of meningitis and then bacterial meningitis is made from analysis of CSF. When meningitis is suspected, the lumbar puncture (LP) becomes an emergency procedure. Table 13-3 demonstrates the CSF findings in bacterial meningitis and distinguishes them from other CNS infections. Figure 13-2 illustrates the common bacteria that cause meningitis in the United States. In countries that do not give children the *Haemophilus influenzae* vaccine, *H. influenzae* meningitis is the most common type for children younger than 5 years.

Almost all patients have an elevated WBC count that may be over 20,000/mm<sup>3</sup>. Neutrophils

are elevated, and there are elevated numbers of immature cells or a “shift to the left.” The blood erythrocyte sedimentation rate (ESR) and C-reactive protein are also elevated.

Neuroimaging does not diagnose bacterial meningitis. Cranial CT scans might be indicated before the LP if intracranial masses or acute hydrocephalus are suspected (see section on CSF in Chapter 3, “Common Neurologic Tests”). Enhancement of the meninges, especially in the basal cistern area, is commonly seen with a gadolinium-enhanced MRI. If neurologic complications develop in the patient, neuroimaging may demonstrate communicating or obstructive hydrocephalus, brain infarctions, or focal areas of brain necrosis across the cortical surface.

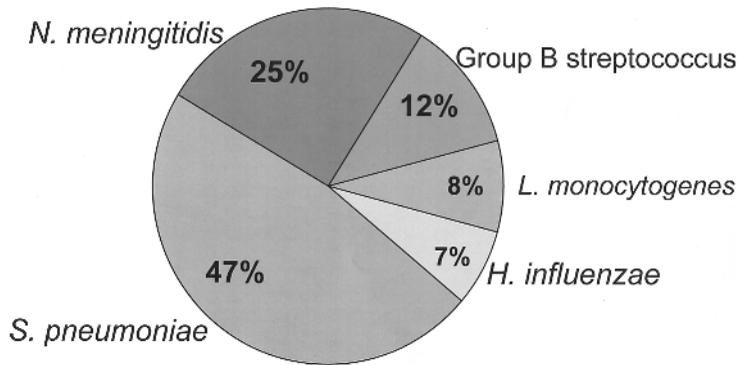
**Principles of Management and Prognosis**

The key to etiologic treatment is the prompt administration of appropriate antibiotics. Without antibiotics, over 95% of patients die. General principles involved in the use of antibiotics are the following: (1) the antibiotic should be given as early in the clinical course as possible; (2) the bacteria must be sensitive to the antibiotic administered; and (3) the antibiotic must cross the blood–CSF barrier and achieve sufficient concentration to kill the bacteria. Once the clinical diagnosis of bacterial meningitis is made, immediate treatment with broad-spectrum antibiotics begins. Based on the patient’s age, predisposing medical condition,

**Table 13-3 Cerebrospinal Fluid Findings in Major Central Nervous System (CNS) Infections\***

	<b>Opening Pressure</b>	<b>White Blood Cells (WBCs)/mm<sup>3</sup></b>	<b>Predominate WBC Type</b>	<b>Protein (mg/dL)</b>	<b>Glucose (mg/dL)</b>	<b>Bacterial or Fungal Culture</b>
<b>Meningitis</b>						
Viral	N	20–1,000	Mononuclear	SI ↑	Normal	Negative
Bacterial	N or ↑	50–5,000	Neutrophils	↑	Low	Bacteria
Tuberculosis or fungal	↑	50–10,000	Neutrophils and lymphocytes	↑	Low	Sometimes positive
CNS syphilis	N	10–1,000	Lymphocytes	↑	Normal	Negative
<b>Brain Abscess</b>	↑	0–20	Lymphocytes	Normal	Normal	Negative
<b>Viral Encephalitis</b>	SI ↑	10–200	Lymphocytes	SI ↑	Normal	Negative

\* Exceptions to these rules often occur. N = normal; SI = slight; ↑ = increase.



**Figure 13-2** Common bacteria that cause meningitis in the United States.

immune status, CSF Gram stain or bacterial antigen tests, and knowledge of types of drug-resistant bacteria in the community, antibiotics are chosen that likely will kill the CSF bacteria. When the bacterium is grown in the laboratory and antibacterial susceptibilities are determined, the antibiotic regimen can be appropriately modified.

The optimal initial antibiotics to be given constantly change; one should consult the latest antibiotic recommendations. Currently, many patients are initially treated with a third- or fourth-generation cephalosporin and vancomycin since the incidence of *Streptococcus pneumoniae* resistance to third-generation cephalosporins is now >15% in most communities. In general, the antibiotics should be administered intravenously for 10 to 14 days. Early administration of corticosteroids for 2 to 4 days has been shown to reduce the death rate and long-term neurologic sequelae in children and adults.

Symptomatic treatment of seizures includes administration of phenytoin until the patient is discharged. If severe obstructive hydrocephalus develops, a ventriculoperitoneal shunt is required.

Meningitis from *Neisseria meningitidis* and *H. influenzae* require chemoprophylaxis of immediate family members and close contacts with rifampin or ciprofloxacin (adults only), as they are at increased risk of developing meningitis.

Mortality ranges from 5% to 25%, depending on the infecting bacteria, age of patient, and predisposing illnesses. In surviving children, 15% have language disorders, 10% mental retardation, 10% hearing loss, 5% weakness or spasticity, and 3% epilepsy. Adults have a similar pattern.

## Brain Abscess

### Introduction

A brain abscess is a localized mass infection within the brain parenchyma. If the abscess develops outside the brain and around the dura, it is called either a subdural empyema or epidural abscess. Brain abscesses most commonly occur from a bacterial infection, but fungi, *M. tuberculosis*, and protozoa can also cause the focal brain infection. Brain abscesses are uncommon, with an incidence of about 1/100,000 persons per year, and develop in both sexes and all ages.

### Pathophysiology

The brain has no normal flora of bacteria or fungi. Microorganisms that cause an abscess reach the brain primarily through the bloodstream or directly from adjacent infected sinuses or mastoid air cells. Less-common routes of entry include depressed skull fractures or following surgical procedures involving the sinuses, calvarium, or brain. Common sources of bloodstream infection include infections of the lungs (bronchiectasis, empyema, and lung abscess), GI tract, urinary system, mouth (dental abscess), heart (acute bacterial endocarditis and cyanotic congenital heart disease), and intravenous drug abuse. In about 15% of patients, no initial source for the brain abscess can be identified.

The location of the abscess depends on the source. Brain abscesses from sinusitis occur in the frontal lobe adjacent to the infected sinus.

Abscesses from mastoiditis develop in the temporal lobe (from upward extension) or occasionally in the cerebellum (from medial extension). The locations of abscesses from a hematogenous route are generally distributed proportional to cerebral blood flow. About 3/4 of brain abscesses are solitary. Multiplicity of abscesses at different locations implies a hematogenous origin.

The brain abscess begins as a small area of brain infection (cerebritis), often located at the gray–white matter junction of the cerebral cortex. Growth of the organism soon results in expansion of the cerebritis, with increasing numbers of neutrophils and mononuclear cells entering the infected site. Necrosis with liquefaction of the center of the abscess then occurs. A variable amount of surrounding cerebral edema contributes to the mass of the abscess. A fibrotic and gliotic response surrounds the abscess, forming a capsule, but the capsule wall is inadequate to control medial expansion of the abscess. If untreated, the abscess expansion continues until the mass is large enough to cause transtentorial herniation (cerebral hemisphere abscess), foramen magnum herniation (cerebellar abscess), or rupture of the abscess contents into the ventricles (ventriculitis).

### Major Clinical Features

The signs and symptoms of a brain abscess are those of an expanding brain mass that develops over 1 to 2 weeks (Table 13-2). Common symptoms at presentation are those of increased intracranial pressure (ICP) and focal neurologic signs. Signs of ICP include headache (75%), lethargy and confusion (50%), nausea and vomiting (50%), and CN palsies (30%). Less-common signs of ICP include papilledema (10%–25%) and stiff neck (25%). Focal neurologic signs (40%) depend upon the abscess location, but hemiparesis, aphasia, homonymous hemianopsia, and ataxia are common. Focal or generalized seizures occur in 33%. Systemic signs are uncommon. Fever is present in less than 1/2 of patients and is usually below 39°C. Depending on the location, the focal neurologic signs may present first, followed by increasing signs of ICP. If the abscess begins in a clinically silent area such as the anterior frontal lobe, the reverse order of symptoms may develop. The abscess continues to expand, produc-

ing a larger mass. Without treatment, the expanding abscess causes ruptures into the ventricle or produces brain herniation.

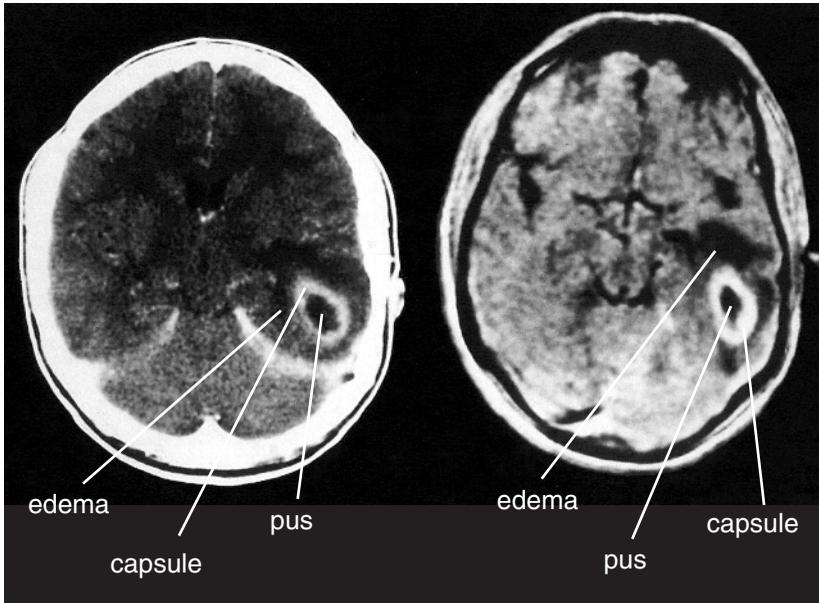
### Major Laboratory Findings

The WBC count is elevated in 60% of patients but the total count is elevated above 20,000 cells/mm<sup>3</sup> in only 10%. The ESR and serum C-reactive protein are often elevated, indicating the presence of a systemic infection. In about 1/2 of patients, the primary source of the abscess can be identified. Biopsy or aspiration material from the distant site can be studied in a manner similar to studying the abscess pus. The most important laboratory tests involve the pus surgically removed from the abscess. The following tests should immediately be performed: (1) stain of abscess material with Gram, Giemsa, and fungal stains, (2) culture of abscess material for anaerobic and aerobic bacteria and fungi, (3) culture of abscess material for *M. tuberculosis* or protozoa if clinical history warrants, and (4) processing of tissue for histologic examination if solid material is present to identify neoplasm, bacteria, fungi, protozoa, etc.

The clinical diagnosis is made by neuroimaging with cranial CT with and without contrast or MRI with and without gadolinium (Figure 13-3). The neuroimaging differential diagnosis includes necrotic or cystic primary and metastatic brain neoplasms, granulomas, subdural empyema, and atypical cerebral infarctions and hematomas. MRI is slightly more sensitive in establishing the diagnosis since it is especially good for identifying early cerebritis, multiple abscesses, abscesses located adjacent to bone, and distinguishing abscess from tumor or other mass.

### Principles of Management and Prognosis

Optimal management of the patient involves (1) prompt reduction of the size of the life-threatening mass (abscess and surrounding cerebral edema), (2) collection of appropriate culture specimens, (3) definitive treatment of the brain abscess with antibiotics and usually neurosurgical drainage or evacuation of the abscess, (4) identification and elimination of the source of the brain abscess, (5) prevention of seizures, and (6) neurorehabilitation.



**Figure 13-3** Brain abscess (computed tomography and magnetic resonance imaging scans).

Reduction of the mass size is best accomplished by stereotactic surgical aspiration of the abscess once it has reached the liquefaction and cavitation stage. Stereotactic surgery using CT or MRI guidance is minimally invasive and provides pinpoint accuracy for aspiration of selected sites. Corticosteroids may be administered briefly to reduce the surrounding cerebral edema but should be stopped as soon as possible since steroids may interfere with the host cellular immune response to the abscess.

The initial antibiotic treatment should be targeted against a wide variety of anaerobic and aerobic gram-positive and gram-negative bacteria. If the patient is immunocompromised or has existing chronic sinusitis or mastoiditis in which a fungal infection is suspected, the addition of antifungal drugs should be considered. Chosen antibiotics should penetrate the blood–brain barrier and abscess wall and not become inactivated by abscess pus. The most common initial therapy is a third- or fourth-generation cephalosporin plus metronidazole for anaerobic bacterial coverage. The duration of antibiotic treatment ranges from 4 to 8 weeks.

Under some circumstances, patients can be treated with antibiotics and without surgery. These

indications include cerebritis without encapsulation, multiple small abscesses in whom the likely bacteria can be isolated from the site of the initial infection source, and abscesses located deep in the brainstem or basal ganglia. In these patients, frequent repeat neuroimaging should be used to monitor for abscess expansion that might then alter the treatment plan.

Administration of phenytoin is given to prevent seizures, which dramatically further elevate the ICP. Rehabilitation after treatment helps minimize neurologic sequelae.

The mortality of a brain abscess remains 10% to 20%. In survivors, 20% to 60% are left with neurologic sequelae that include hemiparesis, aphasia, ataxia, and visual loss. Chronic seizures are common, may be focal or generalized, and may be difficult to suppress with anticonvulsants.

## **Herpes Simplex Virus Encephalitis**

### **Introduction**

Encephalitis is a diffuse infection of the brain parenchyma. Viruses are the most common infec-

tious agents, but bacteria (e.g., general paresis from *T. pallidum*), and protozoa (e.g., toxoplasmosis) also cause diffuse brain infections. There are numerous viruses that cause encephalitis, but herpes simplex virus (HSV) and a group of arboviruses (for *arthropod-borne viruses*) are the most common. Arboviruses are transmitted by mosquitoes or ticks. As such, human infections occur in clusters or epidemics in late spring, summer, and early fall, when the vectors are present. The natural cycle of many arboviruses involves birds and mosquitoes; humans are not part of this life cycle. When a new arbovirus is introduced into an area that has mosquitoes and birds that can become infected by the virus, an epidemic may develop (e.g., West Nile virus in North America). Humans become infected when bitten by virus-infected mosquitoes. Herpes simplex encephalitis (HSE) occurs sporadically year round since the virus is usually latent in the host. In the United States, HSV is the most common cause of sporadic encephalitis and West Nile virus the cause of clustered or epidemic encephalitis.

The severity of the encephalitis depends mainly on the infectious organism. Thus HSV, eastern equine encephalitis, and Japanese B virus cause severe encephalitis while Venezuelan equine encephalitis and California viruses produce mild disease. Most viruses that cause encephalitis infect both neurons and glia. An exception to this rule is poliomyelitis, where the poliovirus selectively infects only neurons involved in the motor system.

HSV type 1 is most often responsible for acquired encephalitis in children and adults. In contrast, type 2 virus is associated with genital herpetic lesions and most often causes acute and recurrent meningitis in children and adults. It also causes encephalitis and disseminated infection in newborn infants who acquire the viral infection during delivery.

### Pathophysiology

HSV type 1 is most often acquired during early childhood as a self-limited stomatitis that is seldom diagnosed. During that infection, the virus travels up the sensory axons of the trigeminal nerve from the mouth to the trigeminal ganglia. In the corresponding ganglion neuron, the virus becomes latent in the nucleus. During latency, no

viral proteins appear on the neuronal membranes, so the host immune system cannot detect and eliminate the virus. From time to time, viral latency breaks and new virus produced in the neuron cell body travels down the axon-releasing virus at the skin, ending where a localized infectious vesicle (fever blister) develops.

How HSV reaches the brain is poorly understood. Since HSE usually develops in healthy individuals who have been previously infected with HSV, activated latent virus appears to reach the brain. One hypothesis proposes that a latently infected neuron in the trigeminal ganglion innervates the base of the brain rather than the face. Should that neuron break latency, the resulting viral infection would develop in the ipsilateral temporal lobe.

Most cases of HSE start in the temporal lobe. The viral infection rapidly produces encephalitis in the medial temporal lobe, then spreads to the opposite temporal lobe and throughout the brain. The pathologic hallmark of all encephalitides is widespread brain inflammation usually characterized by perivascular cuffing (lymphocytes adjacent to cerebral blood vessels) and focal areas of necrosis with secondary gliosis (glial nodules). Commonly HSE is severe enough to produce areas of necrosis and hemorrhage. Viral-infected neurons and glia often develop an intranuclear inclusion body (Cowdry type A inclusion) that can be seen by light microscopy. Intranuclear inclusions are not specific for HSE and can be seen in cells infected with other herpes viruses (varicella-zoster and cytomegalovirus) and rubeola (measles) virus.

### Major Clinical Features

HSE develops equally in both sexes and in all ages without a prodromal illness. Acute encephalitis is characterized by the abrupt onset of fever, headache, and mental obtundation. Table 13-2 lists the most common signs and symptoms for all forms of encephalitis, including HSE. Although HSE begins in the temporal lobe, there are no clinical features that allow its distinction from other viral causes of encephalitis. For example, the presence of a labial fever blister or isolation of HSV from the blister or throat is of no diagnostic value since HSV oral lesions often develop in any ill patient with encephalitis from any cause.

Encephalitis differs from meningitis in that patients present with prominent mental changes and minimal or absent stiff neck.

### Major Laboratory Findings

The peripheral WBC count is often mildly elevated, with a shift to the left. The CSF may be under increased pressure and usually shows a mononuclear pleocytosis ranging from 10 to 200 WBC/mm<sup>3</sup>. Frequently, the CSF contains elevated RBCs that can range over 1,000/mm<sup>3</sup>. The CSF protein level is mildly to moderately elevated, but the glucose level remains normal. Gram stain is negative. CSF viral cultures rarely grow HSV. IgG antibodies to HSV type 1 are present in most older children and adults and HSE does not result in production of immunoglobulin (IgM) antibody. Therefore, the presence of antibody to HSV rarely helps make the diagnosis.

A definitive diagnosis is usually made by detection of HSV DNA in CSF by a PCR test (see Chapter 3, “Common Neurologic Tests”). The CSF PCR assay for HSV is positive in over 95% of HSE patients during the first week of the encephalitis.

The EEG is abnormal in all cases of encephalitis and helps distinguish viral encephalitis from viral meningitis, which usually has a normal EEG. In some patients with HSE, the EEG demonstrates high-voltage complexes that originate from the temporal lobes in a semiperiodic nature that are suggestive but not diagnostic.

The MRI scan is very helpful in HSE. Early MRI images often demonstrate T2-weighted abnormalities in the medial aspect of a temporal lobe, with extension into the subfrontal and insular cortex. Cingulate gyrus involvement is also common. When MRI changes are seen in the medial temporal lobe in a patient with encephalitis, the likelihood of HSE is greatly increased, as arbovirus encephalitis seldom begins in the temporal lobe. CT is less helpful since abnormalities appear a few days later than in an MRI. CT abnormalities include low-density lesions in one or both temporal lobes and areas of hemorrhagic necrosis.

### Principles of Management and Prognosis

Treatment with the antiviral drug acyclovir dramatically improves morbidity and mortality. The

sooner the acyclovir is given, the better the outcome. Patients who are lethargic at the start of therapy do better than those who are comatose. Acyclovir is given in high dosage intravenously usually for 14 days.

In the presence of HSV thymidine kinase, acyclovir is monophosphorylated within a cell. Host cell thymidine kinases then phosphorylates the drug to its active triphosphate state, which then inhibits DNA synthesis. Of note, acyclovir is relatively nontoxic to normal cells and has few side effects, but its administration requires good hydration to prevent renal failure from the drug precipitating in the kidney.

Unfortunately there are no satisfactory drugs for the common RNA viruses (arboviruses, measles, and rabies). Thus treatment for encephalitis from these viruses remains symptomatic.

In the absence of acyclovir treatment, HSE has a mortality rate of 70%. Mortality from encephalitis from arboviruses ranges as high as 50% for eastern equine encephalitis and Japanese B virus to 10% to 15% for West Nile virus and other arboviruses. Currently about 70% of patients with HSE treated with acyclovir survive and 30% of survivors make a good recovery.

## Prion Diseases

### Introduction

Prion diseases are uncommon and occur as Creutzfeldt-Jakob disease (CJD), the juvenile variant of CJD (vCJD), Gerstmann-Sträussler syndrome, fatal familial insomnia, and kuru in humans, scrapie in sheep, and bovine spongiform encephalopathy (mad cow disease) in cattle. These prion diseases are discussed because the infectious agent (prion) breaks the conventional rules for infectious agents and may represent a new class of misfolding diseases. First, the infectious particle is a single unique protein molecule (prion) of 27 to 30 kd whose DNA resides in host chromosome 20. No nucleic acid has been identified that is attached to the protein. Second, the infectious particle is not killed by formalin, ethanol, or boiling but can be destroyed by autoclaving. Third, patients with the illness do not present with typical signs of an infection. They lack fever or elevated WBC counts

and have normal-appearing CSF. Fourth, the host makes no immune response to the infectious protein, so the brain lacks inflammatory cells typical of encephalitis.

### Pathophysiology

Prion diseases occur by three different routes: sporadic, infectious, and hereditary, and all share an abnormal brain protein called a prion. The *PRNP* gene on human chromosome 20 produces a normal cellular protein (PrP<sup>c</sup>) that has a specific 3-dimensional (3-D) configuration that is found in membranes of neurons and other cells. The normal function of the PrP<sup>c</sup> protein is poorly understood. In prion diseases, the normal cellular protein somehow alters its 3-D configuration to become a family of abnormal prion proteins, commonly called PrP<sup>sc</sup>, that all contain the same amino acid sequence. The normal PrP<sup>c</sup> protein has a high  $\alpha$ -helical structure content while abnormal prions have in common a high  $\beta$ -sheet content, but each has a different 3-D configuration. Each different 3-D configuration causes a human disease that has a different clinical picture (phenotype). The probability of the protein misfolding increases if genetic mutations are present at specific DNA sites. The abnormal protein not only causes neurologic disease but also is infectious.

When the abnormal prion enters a normal cell containing only normal PrP<sup>c</sup> proteins, the prion causes PrP<sup>c</sup> proteins to reconfigure their 3-D structure to become identical to the 3-D structure of the abnormal prion. Prions are poorly catabolized by the host cell, accumulate, and eventually kill the cell. While systemic cells dying from prions can be replaced, neurons cannot divide, leading to neurologic disease from a progressive loss of neurons. The abnormal prion is structurally so close to the normal cell protein that the host does not recognize prions as foreign and hence produces no immune response. As such, prion diseases appear like a degenerative disease without inflammatory cells or the production of a specific antibody.

The most common form of CJD is sporadic, in which many neurons have prions. How the body first developed prions remains unclear, but it could begin following spontaneous transformation of a normal PrP<sup>c</sup> protein into a prion. Once CJD develops from any cause, the nervous system becomes infectious. Infectious transmission producing CJD

in the recipient has been shown to occur following transplantation of corneas, pituitary extracts, and dural grafts. There is considerable evidence that the vCJD seen in the United Kingdom can develop, though rarely, from oral consumption of the meat of infected cattle. Finally, CJD as well as other human prion diseases can be autosomal dominant hereditary diseases occurring in families with specific single-site mutations in the *PRNP* gene. Again, these patients are infectious should the above tissues be donated to others.

The pathologic hallmarks of CJD are generalized brain atrophy, spongiform degeneration ( “tiny holes” in the cortex), and widespread gliosis without inflammation. Amyloid plaques are seen in the juvenile variant of CJD and Gerstmann-Sträussler syndrome. Antibody to prions specifically stains amyloid plaques, brain cortex, cerebellum, and tonsils from vCJD patients. Systemic organs are histologically normal.

Prion diseases may represent the first of a new class of misfolding diseases. It is known that yeasts and fungi, when environmental conditions warrant, have some proteins that can alter their 3-D configuration normally to acquire unique properties for the new environment. If vertebrate proteins also can change their 3-D structures normally, then misfolding can occur and lead to disease that would not necessarily be infectious. Currently, Huntington’s, Alzheimer’s, and Parkinson’s disease are potential candidates for this new disease mechanism.

### Major Clinical Features

CJD is the most common prion disease, with an incidence of 1/1 million adults. The majority of cases are sporadic, developing in previously healthy adults with a mean age of 65 years (CJD from a genetic or infectious cause has an earlier age of onset). The onset is insidious but then patients develop a rapidly progressive dementia. Myoclonus appears in over 1/2 of patients as the dementia progresses. Occasionally patients also develop ataxia, visual loss (cortical blindness or homonymous hemianopia), and extrapyramidal or pyramidal signs. Patients lack systemic symptoms of fever, aches, and myalgia. Within 4 to 6 months, patients are severely demented, rigid, mute, and unresponsive.

vCJD appears in children and young adults who have eaten beef of British origin years earlier.

These patients often present with psychiatric symptoms (anxiety, withdrawal, behavior changes, and depression) shortly before dementia and myoclonus develop.

### Major Laboratory Findings

Routine blood tests are normal. Cerebrospinal fluid is under normal pressure and contains no cells and normal glucose and protein. Oligoclonal bands are not seen. The CSF contains a nonprion, chaperone protein called 14-3-3. When seen on electrophoresis, it is characteristic, but not diagnostic, for CJD. An EEG may show characteristic abnormalities, particularly later in the illness. MRI shows progressive brain atrophy and often demonstrates increased signal in the basal ganglia and cortex on a diffusion-weighted image. The later finding is diagnostically helpful.

The prion infectious agent is complicated to isolate and requires incubation in small laboratory animals for months. However, CSF, brain, pituitary, and peripheral nerves that innervate cornea and dura contain infectious prions. Tonsils are infectious in vCJD. The infectious agent does not appear to be present in saliva, urine, sweat, or stool, so isolation of the patient is not necessary. Blood should be considered infectious, but no documented human cases have occurred from blood transfusions.

### Principles of Management and Prognosis

Currently, there is no available treatment to stop disease progression. Death in CJD usually occurs within 6 months of diagnosis and within 2 years

for vCJD and other genetic prion diseases. Since the infectious agent is present in tissues, patients suspected of a prion disease should not donate blood or autopsies organs.

### RECOMMENDED READING

- Davis LE, Kennedy PGE. *Infectious Diseases of the Nervous System*. Oxford, England: Butterworth-Heinemann; 2000. (Comprehensive review of many different CNS infections.)
- Mathisen GE, Johnson JP. Brain abscess. *Clin Infect Dis* 1997;25:763–781. (Good overall review that includes pathophysiology, clinical features, and treatment.)
- Peterson LR, Marfin AA. West Nile virus: a primer for the clinician. *Ann Intern Med* 2002;137:173–179. (Nice review of the clinical features of West Nile encephalitis.)
- Saez-Llorens X, McCracken GH. Bacterial meningitis in children. *Lancet* 2003;361:2139–2148. (Reviews pathogenesis, diagnosis, and treatment of bacterial meningitis in children and, by extension, adults.)
- Sy MS, Gambetti P, Wong BS. Human prion diseases. *Med Clin North Am* 2002;86:551–571. (Good review of prions and the human diseases they cause.)
- Whitley RJ, Lakeman F. Herpes simplex virus infections of the central nervous system: therapeutic and diagnostic considerations. *Clin Infect Dis* 1995, 20:414–420. (Excellent review of clinical features, pathogenesis theories, diagnosis, and treatment.)

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# 14 BRAIN TUMORS

## Overview

The term “brain tumor” refers to a collection of neoplasms of differing cell types, biology, prognosis, and treatment arising as a primary tumor or metastasis. Each year over 17,000 new primary brain tumors are diagnosed in the United States and about 13,000 people die from their disease. Primary brain tumors mainly occur in adults, with a peak incidence in the elderly. Most of these adult neoplasms occur above the tentorium in the hemispheres. Primary tumors develop in infants and children, mainly in the posterior fossa (especially cerebellum), and have different histologic types from those in adults. Most CNS tumors are of glial (astrocytoma more often than oligodendroglioma) origin (>90%) and rarely of neuronal origin (1%).

Brain tumors produce signs and symptoms by 3 mechanisms. The first of these is the tumor location. Since the hemispheres are most commonly affected, common signs include hemiparesis, hemisensory loss, aphasia, and visual field deficits. When the cerebral gray matter is involved, seizures are common and may be either focal or secondarily generalized. As the tumor spreads, cognitive dysfunction is common.

Second, the mass of the tumor can produce signs and symptoms as it expands in a closed intracranial

space. In addition, many tumors release unknown substances that affect the surrounding blood–brain barrier, allowing vasogenic edema to develop. As such, tumors and their surrounding cerebral edema soon produce gradually increasing intracranial pressure (ICP). Increased ICP causes headaches, psychomotor retardation (slowing in amount and speed of cognitive functions coupled with a slowing of motor activities), nausea, vomiting, and papilledema (blurring of optic discs, retinal edema, and flame hemorrhages without loss of vision). The headache is ill defined, intermittent, and may be lateralizing. As the tumor expands, the headache becomes more intense, constant, and increases with coughing or straining at stool. The papilledema results from increased pressure on both optic nerves that impedes axonal flow and venous return from the retina.

Third, as the mass expands, the resulting increased ICP may shift intracranial structures downward enough to produce brain herniation.

## Brain Herniation Syndromes

Brain herniation may occur as a result of downward herniation of the brain through the tentorium (central and uncal herniation), cingulate

gyrus herniation under the falx (subfalcine herniation), or cerebellar tonsillar herniation into the foramen magnum and against the medulla (tonsillar herniation) (Figure 14-1). Death from central brain herniation results from progressive bilateral parenchymal impairment of the diencephalons, leading to ischemia and necrosis of the mid-brain and pons (Duret hemorrhages). Signs and symptoms of progressive central brain herniation include (1) impairment of alertness that progresses to stupor and coma, (2) sighs and yawns that progress to Cheyne–Stokes breathing, then to fixed hyperventilation, and finally to apnea, (3) small pupils (1 to 3 mm) that barely react to light that progress to midposition (3 to 5 mm) pupils that do not react to light, and (4) vestibuloocular reflex (“doll’s eyes” reflex) and ice water caloric test (ice water placed in the external auditory canal) that progress from normal to being nonresponsive (see Chapter 16, “Coma and Cerebral Death”).

Uncal herniation occurs when a lateral hemisphere mass displaces the medial edge of the uncus and hippocampal gyrus through the tentorium. Initially there is dilation of the ipsilateral pupil due to

compression of the CN III, followed by ipsilateral hemiparesis from compression of the cerebral peduncle against the tentorial edge. Compression of the posterior cerebral artery may occur, with ischemia/infarction of the ipsilateral occipital lobe, producing a contralateral homonymous hemianopia. Events then are similar to central herniation.

Tonsillar herniation is due to compression of the cerebellar tonsils against the medulla, producing early nuchal rigidity and head tilt followed by coma and respiratory arrest.

Depending on the tumor’s rate of growth, death can occur when the tumor reaches the size of about 100 grams (~ $1 \times 10^{11}$  cells) or about the size of a golf ball. This is compared with systemic tumor, where death occurs when the tumor reaches about 1,000 grams.

### Cerebral Edema

Cerebral edema, excess fluid present either locally or diffusely in the brain, develops as a result of many pathologic processes, including brain tumors, head

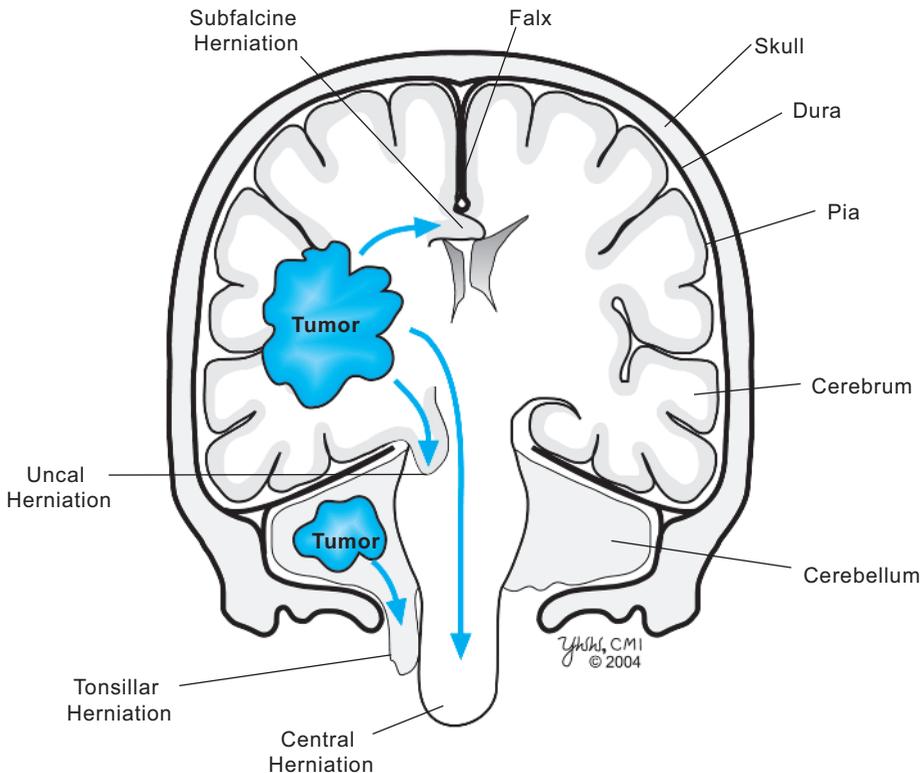


Figure 14-1 Brain herniations secondary to tumors.

trauma, brain abscess and meningitis, anoxia, and some metabolic disorders. Cerebral edema has been divided into three types: vasogenic, cytotoxic, and interstitial. Interstitial edema is uncommon and results in obstructive hydrocephalus with CSF backing into the white matter around the ventricles.

Vasogenic edema is the most common form of cerebral edema and frequently surrounds brain tumors. The edema results from localized dysfunction of the blood–brain barrier, with increased permeability of capillary endothelial cells. Vasogenic edema reduces following administration of corticosteroids. Cytotoxic edema develops from a swelling of neurons, glia, and endothelial cells, usually following hypoxia. Hypoxia causes failure of the adenosine triphosphate (ATP) dependent sodium pump within cells with subsequent accumulation of intracellular sodium and water. Cytotoxic edema is difficult to reduce and does not respond to corticosteroids. Characteristics of vasogenic and cytotoxic edema are listed in Table 14-1. Both types of edema produce a mass effect that can contribute to shifting of brain structures and brain herniation.

## Glioblastoma Multiforme— Malignant Astrocytoma

### Introduction

Glioblastoma multiforme (high-grade astrocytoma) is the most common primary brain tumor in adults, with an annual incidence of 3/100,000 population. Glioblastomas account for over 40%

of all primary brain tumors and cause over 7,500 deaths per year in the United States. This tumor tends to occur in older adults (mean age 55 years).

### Pathophysiology

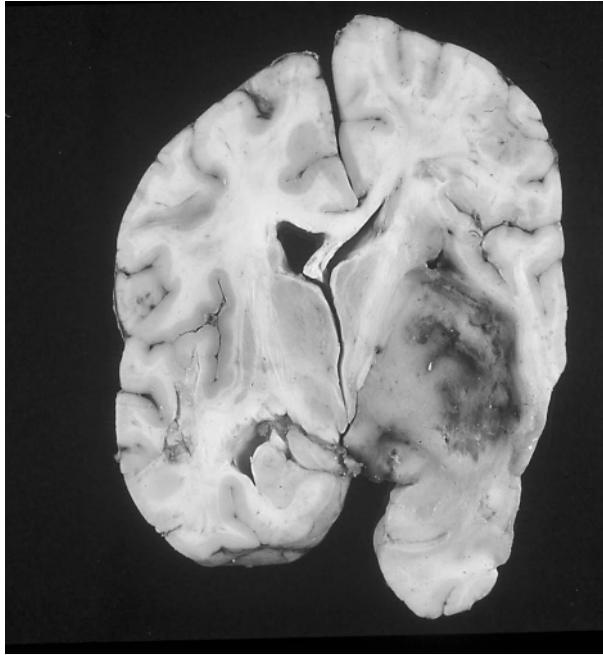
Astrocytomas arise from cerebral astrocytes (glial cells) that abnormally proliferate. Grade 1 astrocytomas are very slow growing, have a normal cellular morphology, and do not induce abnormal vascularity. The most benign astrocytomas typically arise in the optic nerve or brainstem, and patients often survive decades from diagnosis.

Malignant (high-grade) astrocytoma or glioblastoma multiforme usually arises in the cerebral hemispheres and appears grossly as a soft, relatively circumscribed mass that may contain cysts or necrosis (Figure 14-2). The tumor extends many centimeters beyond the apparent gross or neuroimaging margin. Microscopically, the tumor is highly cellular, containing either a uniform cell type or extremely pleomorphic cell types. Multinucleated giant cells are frequently seen. There is extensive neovascularization, with marked proliferation of endothelium of small capillaries feeding the tumor. Astrocytomas rarely metastasize outside the brain.

Tumor cell chromosomes often have extra elements or copies of chromosome 7, resulting in overexpression of the epidermal growth factor receptor (EGFR) gene. Alternately, tumor cells can have deletions in chromosomes 9 or 10 or have mutations in the tumor-suppressor gene *P53*. These abnormalities are felt to be responsible for the malignant growth.

**Table 14-1 Features of Vasogenic and Cytotoxic Brain Edema**

Feature	Vasogenic	Cytotoxic
Pathogenesis	Opening of blood–brain barrier with increased capillary permeability	Cellular swelling of glia, neurons, and endothelial cells
Edema Location	Chiefly white matter	Gray and white matter
Edema Fluid Composition	Plasma filtrate	Increased intracellular water and sodium
Common Causes	Brain tumor, abscess, infarction, trauma, lead encephalopathy, hemorrhages, and bacterial meningitis	Brain hypoxia/ischemia
Corticosteroid Effect	Reduces edema	No edema reduction
Osmotic Agents	Acutely reduces water in normal brain	Acutely reduces water in edematous brain



**Figure 14-2** Pathology of glioblastoma multiforme, with cysts and necrosis. (Courtesy of Blaine Hart, MD)

### Major Clinical Features

Early signs and symptoms include headaches in 50% of patients, altered mental status in 50%, hemiparesis in 40%, aphasia in 15%, visual field loss in 5%, and seizures in 20%. (See “Overview” for details) The seizures may be either focal seizures (usually motor) or secondarily generalized tonic-clonic seizures. Papilledema may be seen on fundoscopy. In the absence of treatment, symptoms of glioblastoma progress relatively rapidly over weeks.

### Major Laboratory Findings

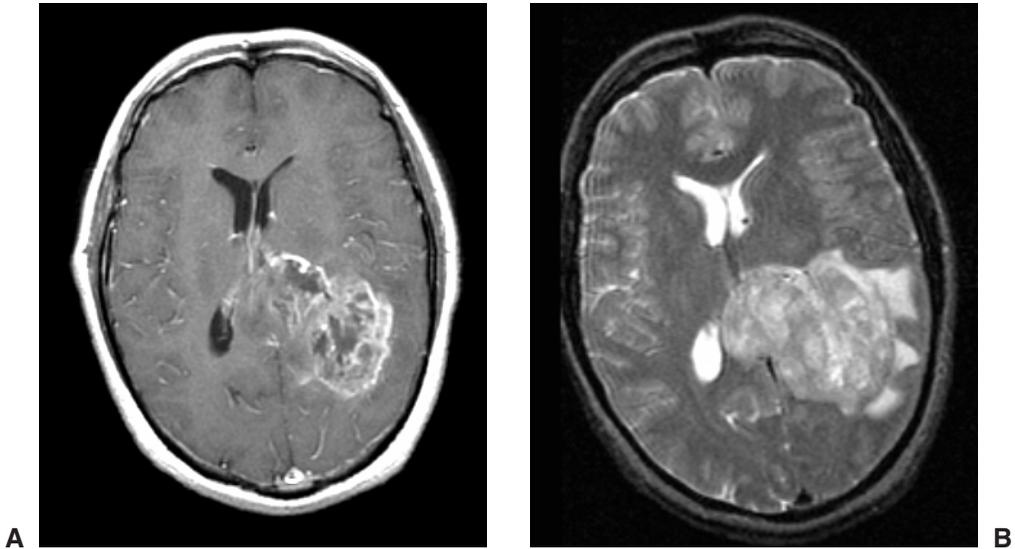
MRI with gadolinium is the test of choice. On MRI the tumor characteristically has low signal intensity on T1-weighted and high signal intensity on T2-weighted images (Figure 14-3). The appearance of gadolinium-enhanced T1-weighted images is that of a central low signal outlined by high-intensity enhancement. Surrounding the high-intensity areas are hypointense signals, representing cerebral edema and tumor infiltration. The extent of cerebral edema varies from tumor to tumor. A CT scan shows variably hypodense or isodense lesions surrounded by hypodense cerebral edema.

The EEG shows focal or extensive slowing ( $\delta$  waves) in the region of the tumor, with varying degrees of spikes at the tumor edge and surrounding edematous brain.

### Principles of Management and Prognosis

Glioblastoma multiforme is always fatal. Thus management aims at slightly prolonging survival and controlling symptoms. Corticosteroids usually reduce the surrounding edema and temporarily improve symptoms and prolong survival for 1 to 3 months. Following steroids, headache lessens, mental status perks up, and focal neurologic signs (such as hemiparesis) improve. Since steroids do not affect tumor growth, the signs and symptoms eventually return. Neurologic side effects of high-dose corticosteroids include psychosis, hyperactivity, irritability, insomnia, and myopathy.

Surgical removal of the main tumor mass (debulking) improves the length of survival and often improves neurologic signs by reducing ICP. Since fingers of the tumor have already spread far beyond the main tumor margins, debulking is never curative. Brain biopsy and minor tumor removal have no effect on survival.



**Figure 14-3** Magnetic resonance image (with gadolinium) of glioblastoma multiforme. (A) T1 with gadolinium; (B) T2 weighted image showing tumor, edema, and midline shift. (Courtesy of Blaine Hart, MD)

Radiotherapy after surgery slightly improves survival compared with surgery alone. Side effects of radiotherapy commonly include anorexia, nausea, hair loss, and fatigue and may include late radiation necrosis of normal brain.

The value of chemotherapy for glioblastoma is controversial. The choice of agent is difficult, as many antineoplastic agents do not cross the blood–brain barrier and thus poorly penetrate the tumor. Antineoplastic agents used alone or in combination have been of limited benefit in improving mean survival time.

In summary, if the glioblastoma is untreated, the mean survival from diagnosis is less than 6 months; adult patients rarely survive longer than 18 months. In adult patients receiving corticosteroids and surgical tumor debulking followed by radiotherapy with or without chemotherapy, 40% to 50% survive 1 year, 10% to 15% survive 2 years, and <1% survive 5 years.

Palliative care minimizes the patient’s discomfort and disability. Headaches can be controlled with surgical debulking, corticosteroids, and analgesics. Anticonvulsants should be given to patients who experience seizures. Cognitive dysfunction can arise from tumor progression, effects of radiotherapy and chemotherapy, corticosteroids, metabolic disturbances, and depression. Treatment efforts should be aimed at the appropriate causes.

## Meningioma

### Introduction

Meningiomas belong to a group of brain tumors that are often called “benign” since they are slow growing, do not invade surrounding structures, and are not histologically malignant. Other common benign tumors include pituitary adenomas, acoustic neuromas, and epidermoid cysts. Meningiomas account for 15% of all intracranial tumors and have an incidence of about 3/100,000 population. The peak incidence is in older adults. Meningiomas are located outside the brain, occur twice as often in women as men, and may be incidental findings at autopsy. Table 14-2 lists their most common locations.

### Pathophysiology

The cause of meningiomas is unknown, but 3/4 have loss of genetic material from chromosome 22 that likely contains a poorly defined tumor-suppressor factor. In addition, 3/4 of meningiomas contain high-affinity, robustly expressed progesterone receptors that may account for the tumor’s higher predilection in women. Various androgen and dopamine receptors of unknown clinical significance occur in 1/2 of these tumors.

**Table 14-2 Location of Meningiomas**

Location	Percent
Falx/parasagittal	25%
Cerebral convexity	20%
Sphenoid wing	20%
Olfactory groove	10%
Suprasellar	10%
Posterior fossa	10%
Other	5%

Meningiomas are felt to arise from arachnoid cap cells and thus may develop at any dural site and receive their blood supply from the external carotid artery. Grossly, the tumor is firm, round, and flat, and has a smooth edge. Histologically the classical tumor is characterized either by a sheet-like syncytial pattern in which the nuclei appear to be lying in an undivided expanse and/or a fibroblastic pattern with fascicles of spindle cells bundled in sweeping, parallel, and gentle curves and whorls throughout the tumor. The whorls may form a nidus for calcifications.

Meningiomas are very slow growing tumors and may be present for more than a decade before they cause symptoms. Their slow growth often allows physicians to simply follow small meningiomas discovered in the elderly.

### Major Clinical Features

As with other brain tumors, meningiomas may present with seizures, headaches, and focal neurologic deficits. Because some meningiomas arise from the base of the skull, cranial neuropathies may occur. Meningiomas in the falx cerebri may present with paraparesis due to bilateral compression of the leg areas of the motor cortex.

### Major Laboratory Findings

CT demonstrates the typical meningioma to be a smooth, lobulated, isodense tumor that is adjacent to dura and enhances uniformly with contrast. Multiple small calcifications are sometimes seen in some tumors. MRI is often less characteristic. On T1-weighted images, the tumor is isointense or

hypointense and on T2-weighted images it is isointense or hyperintense. With gadolinium, T1-weighted images show intense and homogenous enhancement. Some meningiomas show edema in the adjacent brain but rarely do they appear to invade the brain.

### Principles of Management and Prognosis

Since meningiomas are slow growing, many small asymptomatic tumors can be followed safely with periodic neuroimaging. However, when the tumor becomes symptomatic, surgical removal is indicated. Depending on the location, the tumor can be totally excised or partially removed. Total removal has a 10-year recurrence rate of about 10%. For partial resection, about 40% of patients develop major symptoms in the following 10 years. Both radiotherapy and chemotherapy show little to no benefit.

## Pituitary Adenoma

### Introduction

The pituitary lays in the sella turcica, surrounded by the sphenoid bone and covered by the sellar diaphragm. The hypothalamus and optic chiasm lie nearby. The pituitary weighs about 0.6 gm and physiologically enlarges during pregnancy and lactation. It divides into the adenohypophysis (80%) and neurohypophysis (20%). Blood supply mainly comes from portal circulation and lacks a blood–brain barrier.

Tumors of the pituitary can be divided into microadenomas (<10 mm diameter) and macroadenomas (>10 mm diameter) or divided into the cell types that secrete different hormones. Macroadenomas expand above the sella turcica, often affecting the optic chiasm, and may enlarge laterally into the cavernous sinus to entrap cranial nerves. Microadenomas are usually suspected based on hormonal changes in the patient or are incidentally identified on MRI scans performed for other reasons.

### Pathophysiology

Pituitary adenomas account for 10% of all intracranial tumors. The cause of this tumor formation is unknown. Overall, these tumors rarely appear malignant, seldom metastasize, grow slowly, and remain stable in size for years. Some tumors, such as

**Table 14-3 Common Hormone-Secreting Pituitary Adenomas**

	<b>Prolactinoma</b>	<b>Acromegaly</b>	<b>Cushing's Disease</b>
Hormone Secreted	Prolactin	Growth hormone	ACTH
Cell Type	Lactotroph, mammotroph	Somatotroph	Corticotroph
Percent of Cell Type in Normal Pituitary	20%	50%	20%
Tumor as a Percentage of All Adenomas	50%–75%	10%–15%	1%–4%
Major Signs Due to Hormone Secretion in Adults	Women Galactorrhea Abnormal menstruation Infertility Men Hypogonadism with decreased libido and impotence Gynecomastia	Recent extremity growth Arthralgias Excessive sweating Myopathy Jaw malocclusion Carpal tunnel syndrome Hypertension	Weight gain Centripetal obesity Moon facies Skin striae Myopathy Depression and occasional psychosis
Common Tumor Type	Macroadenoma	Microadenoma	Microadenoma
Hormone Tests	Elevated serum prolactin level	Elevated plasma insulinlike growth factor 1 Abnormal glucose tolerance test Random growth hormone levels not helpful	Elevated 24-h urinary glucocorticoid level Dexamethasone-suppression test fails to suppress urinary glucocorticoids ACTH level in petrosal sinus vs. systemic blood has ratio of >2:1
Main Therapy	Bromocriptine	Transphenoidal excision	Transphenoidal excision
Other Causes	Pregnancy, breast feeding, medications		Exogenous corticosteroids, adrenal hyperplasia, and ACTH-secreting tumors elsewhere

ACTH = Adrenocorticotrophic hormone.

prolactin-secreting adenomas, are responsive to hormones or drugs and can expand or shrink in size in response to these compounds. A number of pituitary tumors do not secrete any hormones.

Table 14-3 lists the most common types of hormone-secreting pituitary adenomas and their hormonal features, diagnostic tests, and treatments.

### Major Clinical Features

Macroadenomas with upward growth put pressure on the optic nerves and chiasm, causing visual loss in 50% of patients. The most characteristic visual

sign from damage to the optic chiasm is bitemporal hemianopsia (loss of temporal vision in each eye, which may not be apparent to the patient with both eyes open). There may be optic disk atrophy seen on fundoscopy, but papilledema is rare. Headaches are common (75%) and are likely due to traction on the diaphragma sellae or surrounding dural structures. The character and location of the headache is nondiagnostic. If the adenoma expands laterally into the cavernous sinus, the tumor may entrap CNs III, IV, and VI and the first and second division of CN V, producing diplopia and unilateral upper and mid-facial numbness or

pain. Rarely an adenoma may hemorrhage or infarct, producing pituitary apoplexy with headache, ophthalmoplegia, bilateral visual loss, and drowsiness, leading to coma. Corticosteroid replacement becomes an emergency.

### Major Laboratory Findings

A pituitary tumor (both macro- and microadenoma) has characteristic abnormalities on high-resolution imaging of the sella turcica with MRI and gadolinium or CT with contrast. Common findings include upward convexity of the gland, increased size of the gland, stalk deviation, floor erosion, gland asymmetry, and focal hypodensity or hypointensity in the gland (Figure 14-4). The normal pituitary gland rapidly enhances with gadolinium but the adenoma does not thus enabling its identification.

Specific hormone levels are often elevated. Depending on the tumor type, hormone levels may be difficult to detect in routine blood samples. Thus elevated levels of growth hormone (GH) in acromegaly are best identified by sampling petrosal sinus GH levels via catheterization, which should be twice simultaneous systemic blood GH levels.

Serum prolactin levels are elevated in prolactinomas, but prolactin levels also may be elevated by pregnancy, breast-feeding, marked renal failure,

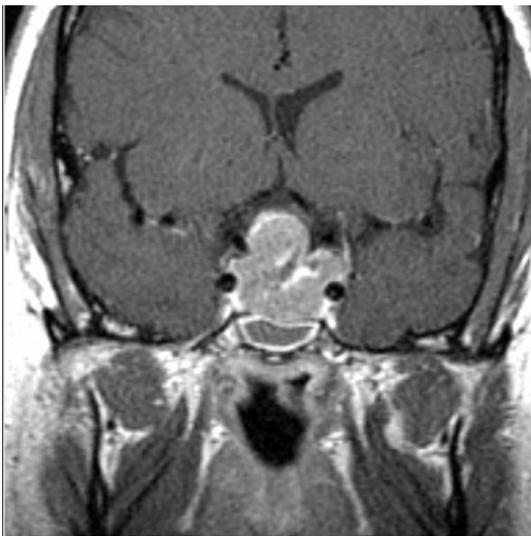
cirrhosis, and dopamine receptor antagonists (chlorpromazine, haldoperidol), estrogens, and opiates. Thus a patient with a prolactinoma should have both an elevated serum prolactin level and an adenoma found on neuroimaging.

### Principles of Management and Prognosis

Goals for treatment are to reduce hormone hypersecretion to normal, shrink tumor size, correct any visual or cranial nerve abnormalities, and restore any abnormal pituitary function. Except for prolactinomas, surgical removal of the macroadenoma is commonly required to preserve vision. About 75% of patients with surgery are cured (total tumor removal observed on MRI and return of involved pituitary hormones to normal blood levels).

Prolactinomas dramatically respond to dopamine agonists (bromocriptine), with a prompt reduction in serum prolactin levels, shrinkage of the tumor, and disappearance of the signs and symptoms. The effect of bromocriptine administration persists for years to decades. Thus administration of bromocriptine usually precludes the need for surgery even when the tumor is a macroadenoma affecting the visual system. However, if the drug is stopped, prolactin levels again elevate and the tumor again grows.

Radiotherapy may reduce growth of the macroadenoma but usually does not stop hormone secretion. Chemotherapy has not been beneficial.



**Figure 14-4** Magnetic resonance imaging scan of pituitary adenoma. (Courtesy of Blaine Hart, MD)

## Cerebral Metastases

### Introduction

Brain metastases are neoplasms that originate in tissues outside the brain and spread secondarily to involve the brain. Of cancer patients, 25% develop brain metastases. As such, cerebral metastases are the most common type of brain tumor in adults. There are more than 100,000 brain metastases annually in the United States. Of these metastases, 80% are supratentorial, 15% are cerebellar, and 5% are located in the brainstem or spinal cord. In addition, 25% of metastases are discovered before or at the time of diagnosis of primary tumor; 60% develop in the next 1 to 6 months, and 10% in months 7 to 12. About 5% develop more than 1 year after the primary tumor is diagnosed.

The most common sources of intracranial metastases are the lung, breast, GI or genitourinary tracts, skin (melanoma), and leukemia. For unknown reasons, a few cancers, such as prostate, uterine, and ovarian, seldom metastasize to the brain. At the time of diagnosis, 1/3 of metastases are single and 2/3 are multiple. However, only 1% of cerebral metastases that are solitary have not metastasized elsewhere in the body. In addition, it is common for a patient with an initial single metastasis subsequently to develop other cerebral metastases.

### Pathophysiology

Most metastases arrive via the blood stream and commonly lodge at the gray–white matter junction, particularly in watershed areas of the cerebral hemispheres. A few metastases reach the spinal cord via retrograde flow via the veins in Batson’s plexus or by extension into the brain from dural or skull metastases. The tumor embolus begins to grow and produces angiogenesis factors that stimulate new vessel formation to supply blood to the tumor bed. These new blood vessels lack a blood–brain barrier. Brain metastases cause considerable vasogenic edema surrounding the tumor that may exceed the size of the tumor. Thus the mass effect of even small metastases may be considerable.

Metastases produce clinical symptoms through several mechanisms. The most common is displacement of brain tissue by the rapidly growing tumor and the adjacent cerebral edema. The displacement causes vessel compression and ischemia, alterations in normal anatomy, and disruption of extracellular fluid spaces. If the tumor is located in the eloquent cortex, the tumor itself may destroy critical neurons and cause symptoms. A metastasis may suddenly become necrotic, hemorrhage, rapidly expand in size, and produce an abrupt increase of symptoms. The tumor may “irritate” adjacent cerebral cortex neurons, triggering focal seizures. Finally, the mass effect of the tumor and cerebral edema may trigger brain herniation (see “Overview”).

Cerebral metastases must be distinguished from other brain lesions such as a primary brain tumor, cerebral hemorrhage, cerebral infarction, and brain abscess. In autopsy series, 5% to 10% of lesions thought to be a solitary metastasis had another etiology.

**Table 14-4 Presenting Signs of Brain Metastases**

Sign	Percent
Impaired Cognition	60%
Hemiparesis	60%
Headache	50%
Aphasia	20%
Hemisensory Loss	20%
Seizures	20%
Papilledema	20%
Visual Field Cut	10%
Stupor or Coma	5%

### Major Clinical Features

Cerebral metastases are usually symptomatic, but a few are discovered at autopsy. Over 2/3 of patients have neurologic signs and symptoms that are similar to other mass lesions (Table 14-4). Seizures are usually focal motor, some of which become secondarily generalized. As metastases expand and produce increased ICP, deterioration of mental status develops and brain herniation may occur.

### Major Laboratory Findings

MRI with gadolinium enhancement is the best diagnostic test. A negative test essentially rules out cerebral metastases. T1-weighted images may not show a small lesion unless there is hemorrhage, but areas of low intensity from the edema may be seen. T2-weighted images show areas of increased intensity that encompass both the tumor and surrounding edema. T1-weighted images with gadolinium show a heterogenous or ring-enhancing lesion, usually with surrounding edema. Shifting of brain structures from the tumor mass effect commonly are seen on all images. A careful search for other metastases should be made, as all lesions are not the same size.

### Principles of Management and Prognosis

Surgical removal of the metastasis only occasionally is helpful in markedly prolonging life. Surgery should be considered when the diagnosis is in

doubt or when the patient is in good overall health, the primary tumor is small and responding to treatment, and there are no other critical systemic metastases.

Dexamethasone reduces the cerebral edema and often dramatically improves the patient's symptoms for 1 to 2 months. The addition of whole-brain or localized radiation therapy to the metastases adds a few more months of survival, but the patient must undergo the complications of radiation and a month of therapy. Chemotherapy appears to add little to survival, but the patient often receives systemic chemotherapy for the primary tumor.

In summary, the median survival without any treatment is 1 to 2 months from the discovery of the brain tumor. With corticosteroids, the survival extends to 2 to 4 months. The median survival with steroids plus radiotherapy is between 3 and 6 months, with 10% surviving 1 year.

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# 15 SEIZURES AND STATUS EPILEPTICUS

## Overview

Single seizures occur in about 5% of the population. Nearly 2 million individuals in the United States (~1%) have epilepsy; 100,000 new cases of epilepsy are diagnosed annually. An epileptic seizure is the behavioral manifestation of abnormal brain neuronal activity. Recurrent seizures secondary to brain disease or dysfunction define epilepsy, which is characterized by recurrent, usually transient, abrupt episodes of disturbed brain function with combinations of loss of consciousness, altered psychic function, and convulsive movements.

## Pathophysiology of Seizures

The genesis of a seizure remains poorly understood. Normal brain function, awake or asleep, produces an organized, yet nonsynchronous, EEG pattern. A seizure, however, results from a paroxysmal high-frequency or synchronous low-frequency electrical discharge that can arise from almost any part of the cerebral cortex (i.e., not the cerebellum, brainstem, or spinal cord). A seizure begins as a spike discharge seen on the EEG and results from thousands of localized pyramidal neurons depolarizing synchronously. Based on experimental mod-

els of epilepsy, the event is thought to involve a reduction in cortical inhibition mediated by GABA, combined with divergent excitation, probably mediated by glutamate. In a focal seizure, the synchronously depolarizing neurons remain localized, while in a generalized seizure, the synchronous depolarizations are present throughout both hemispheres. Why a seizure terminates also is unknown but it likely is not due to exhaustion of neuronal energy-producing substrates.

## Etiologies of Seizures

It is important to remember that *a seizure is a symptom and not a disease*. Any individual can experience a seizure under certain conditions, such as marked hypoxia, severe hypoglycemia, very high fever, or if given an electrical shock to the head (electroconvulsive therapy). It is likely that unknown genes determine some people's susceptibility to developing a seizure. In addition, numerous other disorders that affect the brain can cause seizures. The most common causes of seizures vary by age (Table 15-1) and include brain tumors, strokes, metabolic diseases, drug reactions, drug withdrawal, and infections. In some patients, no cause is found (idiopathic epilepsy).

**Table 15-1 Common Causes of Seizures by Age**

Age Range	Major Causes
Infant	Birth injury, hypoxia/ischemia, congenital malformations, and congenital infection
Childhood	Febrile seizures, central nervous system infection, head trauma, birth injury, and idiopathic origin
Young adult	Head trauma, drugs, withdrawal from alcohol or sedatives, and idiopathic origin
Elderly	Strokes, brain tumor, cardiac arrest with hypoxia, and metabolic origin

## Electroencephalogram

An EEG commonly helps classify the individual's type of epilepsy (see Chapter 3, "Common Neurologic Tests"). Patients rarely experience a seizure during a routine EEG. However, it can provide confirmation of the presence of abnormal electrical activity, information about the type of seizure disorder, and the location of the seizure focus. On a single routine wake-and-sleep EEG, only 50% of epilepsy patients will have an abnormal tracing. The spike is the EEG sign of hypersynchronous activation of a population of neurons that could develop into a seizure. Unfortunately, at least 10% of epilepsy patients never have an abnormal EEG and 2% of normal individuals who never experience a seizure will have epileptiform abnormalities on their EEG. Therefore, the routine EEG cannot rule in or rule out epilepsy, thus the diagnosis of epilepsy remains a clinical function.

## Seizure Classification

There are several classifications for types of epilepsy, which are based on clinical seizure types and/or EEG findings. Seizures are classified as partial or generalized. Generalized seizures involve the both hemispheres early in the seizure. The most common types of generalized seizures are primarily generalized tonic-clonic (grand mal) seizures and absence (petit mal) seizures. Partial seizures involve only a portion of the brain at their onset.

The most common types of partial seizures are simple partial seizures, complex partial seizures, and partial seizures that become secondarily generalized. Table 15-2 outlines the clinical features of these seizure types. Properly classifying the type of epilepsy and determining the cause of the seizures allows a better prognosis and enables selection of the best anticonvulsant medication to control the seizures.

## Primarily Generalized Tonic–Clonic Seizures and Secondarily Generalized Partial Seizures (Grand Mal Seizure)

### Introduction

These seizure types are common and occur in both sexes and at all ages past the newborn period. To the patient, a primarily generalized seizure and a secondarily generalized partial seizure often appear the same (grand mal seizure). However, the presence of a warning or aura suggests the seizure began focally and secondarily generalized. An aura identifies the part of the brain that malfunctioned first and is in fact a partial seizure. Generalized seizures may be idiopathic (particularly primarily generalized seizures) or due to many brain diseases (particularly secondarily generalized partial seizures) (Table 15-1). Primary generalized seizures usually begin in adolescence while secondarily generalized seizures may begin at any age but especially in adulthood.

### Major Clinical Features

Nearly 50% of patients experience an aura that is identical in characteristics from seizure to seizure. The aura lasts seconds and commonly is described as a sinking, rising, gripping, or unnatural sensation that may be accompanied by movements such as head and eye turning. Occasionally, patients will experience an aura without generalizing, especially if taking anticonvulsants. The patient often remembers the aura after the seizure is over.

When the generalized seizure begins, consciousness is always lost and there is no memory of the seizure event. In the tonic phase, the body and limbs stiffen for 20 to 30 seconds. If the patient is

**Table 15-2** *Principal Seizure Types and Their Clinical Features*

Type of Seizure	Clinical Features
<b>Generalized seizure</b>	
Primarily generalized seizure (tonic-clonic or grand mal)	Loss of consciousness occurs without warning, marked increase in all muscle tone (tonic) for about 20–30 seconds followed by rhythmic (clonic) jerks with a gradual slowing or rate and abrupt stopping after 20–60 seconds. Patient is unconscious during and immediately after seizure and slowly recovers over minutes to 1 hour. Tongue biting and urinary incontinence are common. Patient has no recall of actual seizure event.
Absence seizure (petit mal)	Rapid onset of unresponsiveness that lasts an average of 10 seconds. There often is staring that may be associated automatisms (eye blinking or lip movements), an increase or decrease in muscle tone, and mild jerks. Recovery is immediate but there is no recall of event. Hyperventilation often precipitates seizure. Patients are 3–20 years of age.
<b>Partial seizure</b>	
Simple partial seizure (focal)	Signs and symptoms may be motor (twitching of hand, arm, face, legs, or trunk) sensory, autonomic, or rarely psychic and depend on the location of the seizure focus. Consciousness is not impaired. Focal seizures recur at the same location and should not move about. Seizures may last seconds to many hours.
Complex partial seizure (temporal lobe or psychomotor)	Seizure may begin with or without a warning or aura, or with stereotyped motor, sensory, autonomic, or psychic signs or symptoms. Consciousness is impaired and patient does not recall actual seizure. During seizure that usually lasts 1–3 minutes, patient may sit, walk, mumble, and often exhibit autonomic acts such as lip smacking and repetitive hand jesters. Seizure is usually followed by a period of confusion of 5–20 minutes.
Secondarily generalized complex partial seizure (tonic-clonic or grand mal)	Seizure begins as a complex partial seizure (above) and then is followed soon by a generalized seizure. Thus the patient usually has a warning (aura) that culminates in a tonic-clonic seizure.

standing, he or she will fall like a log, often resulting in traumatic injuries. If air forces out the closed glottis, a grunting sound may occur. Patients may also bite their tongue, lip, or cheek and become incontinent of urine. Occasionally in the elderly, the tonic phase may be severe enough to cause a compression fracture, usually involving a thoracic vertebra. Since breathing does not occur during the tonic phase of the seizure, blood may become sufficiently oxygen desaturated to make the patient temporarily cyanotic (blue).

In the clonic phase, rhythmic jerking of the limbs begins in rapid synchrony that slows in intensity and frequency over 20 to 40 seconds. Usually the jerking then abruptly ceases and the seizure ends.

The postictal period lasts for minutes to over an hour but may be longer following a prolonged seizure or multiple closely spaced seizures. The patient is unconscious initially and then is difficult to arouse and confused for a time. The patient

often sleeps following the seizure, which can cause witnesses to describe the seizure as lasting an hour or more.

Seldom does a physician witness a seizure, so the diagnosis must be made by the history obtained from a witness and the patient. Disorders that must be distinguished from a seizure include syncope, migraine, transient ischemic attack, nonepileptic seizure (psychogenic nonepileptic seizure), rage attacks, Meniere's disease attack, and severe movement disorders. In children, breath-holding spells, night terrors, and pallid infantile syncope must also be considered.

Syncope is suggested by the onset always occurring when the patient is erect (seizures occur in any position). Before fainting, the patient usually has a feeling of being "light-headed" or of impending faint that may be accompanied by loss or darkening of vision. Syncope is brief (10–20 seconds) and results in loss of muscle tone so patients collapse with less chance of hurting themselves. Syn-

cope seldom causes muscle twitching, which, if present, should always be very brief (a few seconds). Syncope does not cause postictal confusion.

Nonepileptic seizures should be considered when the patient has (1) complex, prolonged, and variable warnings, (2) nonsymmetrical limb movements, (3) nonrhythmic or semipurposive limb movements, (4) prolonged limb movements that subside and then amplify, (5) no postictal confusion, and (6) memory of the event.

Following a first seizure, the physical examination should search for other findings suggestive of the cause. There should be a search for signs of head trauma, infections of ear, sinuses, brain or meninges, congenital abnormalities (like tuberous sclerosis), focal or diffuse neurologic abnormalities, alcohol or drug abuse and cancer.

### Major Laboratory Findings

In general the following tests are usually performed on a new seizure patient with a normal neurologic examination: serum electrolyte and liver function tests, hemogram, neuroimaging, and an EEG done at least 48 hours after the seizure. MRI is preferred over CT because it can detect small masses and mesial temporal sclerosis. Seldom are major blood or CSF abnormalities found. Elderly patients are more likely to have abnormalities on neuroimaging to account for the seizure etiology.

### Principles of Management and Prognosis

Management of epilepsy should be directed toward preventing future seizures and eliminating or controlling the cause. If this is the first seizure, a decision whether to administer anticonvulsants must be made based on the neurologic exam and EEG. Several studies suggest the risk of developing subsequent seizures is 25% to 50%. The risk becomes higher if there is a history of brain contusion or familial epilepsy and if neuroimaging identifies a brain mass or the EEG is very abnormal.

Anticonvulsants all inhibit excessive neuronal activity by (1) blockade of voltage-gated sodium channels, (2) indirect or direct enhancement of inhibitory GABA neurotransmission, and (3) inhibition of excitatory glutamatergic neurotransmission. In Table 15-3, the major anticonvulsants, first-line seizure indications (most effective drugs with least toxicity), mechanisms of action, and

common toxicities are listed. For generalized seizures, the first-line anticonvulsants are valproate, phenytoin, and lamotrigine. About 2/3 of patients can be well controlled with anticonvulsants. If seizure control is not achieved with the first drug, a second drug should be substituted. If the patient is compliant in taking the medication, success with anticonvulsants is seldom achieved if the third drug trial fails. Some of these patients benefit from 2-drug regimens or from alternate methods such as vagal nerve stimulators or surgical removal of a seizure focus.

All states require individuals with a driver's license to notify the motor vehicles department following a seizure and most prohibit driving for 6 to 12 months after the last seizure.

The decision when to stop anticonvulsants is complex; most patients should continue their anticonvulsant for at least 2 years after their last seizure. Reasons to discontinue anticonvulsants are to prevent drug interactions, side effects, risk of teratogenicity if pregnancy is desired, and cost of medication. Factors to consider anticonvulsant continuation include the social stigma of a seizure and the risk of another seizure, which would result in loss of driving privileges for 6–12 months.

## Absence Seizure (*Petit Mal Seizure*)

### Introduction

Primarily generalized absence seizures or petit mal epilepsy has an onset between the ages of 3 and 12 years. This type of seizure disorder has been considered “benign” as it produces brief seizures that do not cause loss of muscle tone (falling) and often spontaneously subside in adulthood.

### Pathophysiology

The etiology of absence seizures is unknown. Since the EEG shows the onset to be simultaneous, with synchronous 3-Hz spike and wave discharges diffusely in both hemispheres, the origin is thought to be in deep diencephalic structures with early spread of the seizure throughout both hemispheres.

### Major Clinical Features

The typical seizure begins with arrest of speech and the abrupt onset of loss of consciousness but

**Table 15-3 Major Anticonvulsants**

Anticonvulsant	Main Seizure Indications	Likely Mechanisms of Action	Major Side Effects*
Phenytoin	Generalized and status epilepticus	Inhibits voltage-dependent sodium channels in a voltage- and use-dependent manner	Nystagmus, ataxia, gum hyperplasia, and hirsutism
Valproate	Generalized, complex partial, and absence	Inhibits voltage-dependent sodium channels in a voltage- and use-dependent manner plus other mechanisms	Gastrointestinal (GI) distress, ataxia, weight gain, and hepatic dysfunction
Carbamazepine and oxcarbazepine	Complex partial	Inhibits voltage-dependent sodium channels in a voltage- and use-dependent manner	Ataxia, dizziness, diplopia, and blood dyscrasia
Lamotrigine	Generalized	Inhibits voltage-dependent sodium channels in a voltage- and use-dependent manner	Abnormal thinking, ataxia, dizziness, and nausea
Ethosuximide	Absence	Blocks voltage-dependent calcium channels that affect T currents	Headache, GI distress, ataxia, and blood dyscrasia
Lorazepam and diazepam	Status epilepticus	Increases GABA-mediated inhibition by affecting the GABA <sub>A</sub> -receptor complex and increasing open-time GABA-activated chloride channels plus increases the frequency of opening of GABA-activated chloride channels	Hypotension, respiratory depression, and secondary cardiac arrhythmias when given intravenously
Vigabatrin	Infantile spasms	Inhibits GABA transaminase, resulting in increased brain GABA levels	Headache, irritability, depression, and confusion

\* Most anticonvulsants are metabolized by the liver, cause sedation to varying extent, cause idiosyncratic rashes, and are teratogenic.

GABA =  $\gamma$ -aminobutyric acid.

does not cause loss of muscle tone and falling. The individual often stares and has eye blinking and minor body jerks for 10 to 30 seconds. The individual then becomes alert but does not recall the episode. The seizures may occur in clusters and are often precipitated by hyperventilation. In school, teachers may think the child is daydreaming or deliberately not paying attention.

### Major Laboratory Findings

The EEG is diagnostic and usually shows generalized 3-Hz spike and wave discharges that can be induced with hyperventilation. Atypical absence seizures can occur with EEG discharges slightly faster or slower than 3 Hz; these may coexist with other seizure types. Neuroimaging is normal.

### Principles of Management and Prognosis

First-line treatment choices are valproate and ethosuximide for typical absence seizures and valproate for atypical absence seizures. In young adulthood, absence seizures stop in about 2/3 of patients. In the remaining patients, absence seizures may progress to primarily generalized seizures or atypical absence seizures.

### Infantile Spasms (West's Syndrome)

#### Introduction

A triad of infantile spasms, hypsarrhythmia on EEG, and mental retardation characterize West's syndrome. Infantile spasms affect 1 in 3,000 live

births. The seizures begin in the first year of life, with a peak onset between 2 and 8 months.

### Pathophysiology

The pathophysiology of infantile spasms and hypsarrhythmia is unknown, but most cases are associated with nonprogressive single or multiple prenatal and postnatal cortical lesions that include cerebral malformations, congenital infections, vascular malformations, metabolic disorders, asphyxia, leukomalacia (abnormal softening of white matter), kernicterus (deposition of bile pigment in deep brain nuclei with degeneration from neonatal jaundice), head trauma, and intracranial hemorrhage.

### Major Clinical Features

Infantile spasms or salaam seizures are characterized by brief, symmetric contractions of neck, trunk, and limb muscles. The spasm may involve groups of muscles (usually both extensor and flexor muscles) or an isolated muscle. Eye deviation, nystagmus, and interrupted respiration are common during the spasm. The spasm is usually followed by a brief tonic phase. The spasms occur in clusters of up to 100 and are most common during sleep or upon arousal. Cognitive disorders may include mental retardation, speech delay, visuo-motor apraxia, and autism.

### Major Laboratory Findings

The EEG classically shows hypsarrhythmia—random, high-voltage slow waves and spikes that vary from moment to moment in location and duration. During sleep the EEG may show a burst-suppression pattern. The more severe the EEG pattern, the more frequent and severe are the infantile spasms.

### Principles of Management and Prognosis

Empirically, adrenocorticotrophic hormone (ACTH) and vigabatrin (not available in the United States) have been found to reduce the frequency of infantile spasms. Both drugs are most effective when given as soon as the infantile spasms begin, but neither drug has been proven to improve the long-term outcome of affected children.

Infantile spasms disappear at 1 at 5 years whether or not the child received treatment. However, the outcome for most children with West's syndrome is poor. About 1/3 die before the age of 3 years and  $\frac{3}{4}$  have moderate-to-severe mental retardation. Of these children, 1/2 progress to experiencing tonic-clonic, atonic, and simple partial seizures and many of these children have EEG patterns suggestive of the Lennox-Gastaut syndrome—a difficult-to-treat form of childhood epilepsy. Good prognostic factors include normal development until seizure onset, cryptogenic cause, and mild hypsarrhythmia.

## Complex Partial Seizure (Localization-Related, Temporal Lobe, or Psychomotor Seizure)

### Introduction

About 450,000 individuals have complex partial seizures. They are particularly common in young adults. In about 80% of cases, the onset is in the temporal lobe, with about 20% developing seizures in the frontal lobe. Nearly 30% of patients may have a mass (tumor, arteriovenous malformation, hamartoma, etc.) identified in either the temporal or frontal lobe. However, the most common etiology is mesial temporal sclerosis.

Mesial temporal sclerosis usually develops in older children and adolescents and is characterized by progressive loss of neurons and gliosis in one hippocampus. It can be identified as a hyperintensity of the hippocampus on T2-weighted MRI images, which over years proceeds to atrophy. The pathogenesis remains unclear but may follow subtle brain damage (head trauma, meningitis, and hypoxia) that occurred in infancy or earlier in childhood. Patients with mesial temporal sclerosis often experience frequent complex partial seizures that do not respond to anticonvulsant medication. However, anterior temporal lobectomy may be curative in 75% of patients with mesial temporal sclerosis.

### Pathophysiology

The seizure genesis is felt to be similar to that of generalized seizures. The striking behavioral

abnormalities are felt to occur because the seizure rapidly spreads in the temporal lobe to affect the limbic system. It is recognized that complex partial seizures are often more difficult to control adequately than are other seizure types, but the explanation is unknown.

### Major Clinical Features

The majority of patients experience an aura, often recalled as a rising or falling sensation in their abdomen, disgusting smell, or limb jerks immediately prior to the seizure. The seizure often begins with cessation of verbal activity associated with a motionless stare. Patients do not normally respond to verbal or visual stimuli. Automatisms may occur that are gestural (picking at objects, repetitive hand-washing movements) or oral (lip smacking), and the patient may wander aimlessly. These movements tend to be stereotyped for each patient and occur with most seizures. Purposeful movements or violence is unusual. Planned activities, such as finding a gun, loading it with bullets and shooting someone, have never been felt to be due to a complex partial seizure. The ictal event (seizure) lasts only 1 to 3 minutes, followed by a period of postictal confusion that usually lasts 5 to 20 minutes. The patient does not recall events during the seizure.

### Major Laboratory Findings

The EEG is often helpful in establishing the diagnosis, particularly when interictal spikes are identified as coming from the temporal or frontal lobe. Because the temporal lobe and underside of the frontal lobe are distant from EEG electrodes, it is difficult to find spikes in some patients. Use of sleep deprivation and special nasopharyngeal and sphenoidal electrodes may improve diagnostic yield.

The MRI scan is often performed with special views of the hippocampus to demonstrate mesial temporal sclerosis. In 30% the cause for complex partial seizures is found.

### Principles of Management and Prognosis

Management is aimed at controlling the complex partial seizures and removing the etiology of the seizures. First-line drugs are carbamazepine,

oxcarbazepine, and phenytoin. Anticonvulsants adequately control about 50% of patients, which is less than that for primarily generalized seizures.

Patients with mesial temporal sclerosis who fail to respond to anticonvulsants are candidates for anterior temporal lobectomy if the seizures are coming from only one temporal lobe. Following surgical removal of the anterior 2/3 of the involved temporal lobe, over 80% of patients have a marked reduction in seizure frequency and 60% are cured.

## Status Epilepticus

### Introduction

A widely accepted definition of status epilepticus is more than 30 minutes of continuous seizure activity or 2 or more sequential seizures without full recovery of consciousness between seizures. The incidence in the United States is about 125,000 cases annually. Each year 55,000 deaths occur that are associated with status epilepticus, which has the highest incidence in the first year of life and in the elderly, though the elderly have the highest mortality rate. Over 10% of adults with their first seizures present in status epilepticus. Table 15-4 lists the etiologies for status epilepticus.

### Pathophysiology

Presumably the seizures are initiated by the same mechanism as with all seizures. However, status epilepticus involves a failure to terminate the

**Table 15-4 Etiologies of Status Epilepticus**

<b>Etiology</b>	<b>Frequency</b>
Low Anticonvulsant Level	34%
Cerebrovascular Accident	22%
Hypoxia/Anoxia	18%
Metabolic Cause	15%
Drug Overdose	13%
Alcohol Related	13%
Central Nervous System Infection	10%
Brain Tumor	7%
Other	5%

seizure. Experimental studies find this failure can arise from abnormally persistent, excessive excitation or ineffective recruitment of inhibition. Standard drugs used for status epilepticus are more effective if given in the first hour of status.

Status epilepticus can cause cerebral injury, especially in limbic structures such as the hippocampus. During the first 30 minutes of seizures, the brain is able to maintain homeostasis through increases in blood flow, blood glucose, and oxygen utilization. After 30 minutes, homeostatic failure begins and may contribute to brain damage. Hyperthermia, rhabdomyolysis, hyperkalemia, and lactic acidosis develop from constant widespread muscle firing. After 30 minutes, other signs of decompensation may develop, including hypoxia, hypoglycemia, hypotension, leukocytosis, and poor cardiac output: However, seizure activity itself appears sufficient to cause brain damage. One mechanism of damage is glutamate-mediated excitotoxicity, particularly in the hippocampus. The normal concentration of calcium outside of neurons is at least 1,000 times greater than that inside of neurons. During seizures, the receptor-gated calcium channel is opened following stimulation of the *N*-methyl-*D*-aspartate (NMDA) receptor by glutamine. This enables intracellular calcium levels to rise potentially to cytotoxic levels.

### Major Clinical Features

Initially patients are unresponsive and have clinically obvious seizures with tonic, clonic, or tonic-clonic limb movements. With time the seizure activity is less obvious. Patients may show only small-amplitude twitching movements of the face, hands, and feet and nystagmoid jerking of the eyes. If the seizure-induced movements stop, the patient remains unresponsive or very confused and the next seizure begins.

On neurologic exam the patient will not respond to verbal commands. He or she will have increased or decreased muscle tone, no purposeful limb movements, and will frequently demonstrate Babinski signs. In general, the neurologic signs will be symmetrical.

There are occasional patients who present with constant confusion, impaired awareness, and able to move limbs and walk that have a type of status epilepticus called nonconvulsive status epilepticus

(complex partial status epilepticus). In these patients, a persistently and specifically abnormal EEG establishes the diagnosis.

### Major Laboratory Findings

A marked leukocytosis (WBC count  $>20,000/\text{mm}^3$ ) without an increase in bands occurs due to loss of margination of WBCs rather than production from bone marrow as seen in an infection. As a consequence of prolonged seizures, the patient develops elevated serum potassium, metabolic acidosis (pH  $<7.0$ ), and varying degrees of hypoxia. A screen of toxins and anticonvulsant levels that are low or absent also may establish the cause.

The EEG is always severely abnormal, showing continuous or nearly continuous spike and wave complexes. The findings on neuroimaging depend on the etiology of the status epilepticus, as status epilepticus of unknown cause may have initially normal neuroimaging.

### Principles of Management and Prognosis

The goal is to stop the seizures from status epilepticus, identify and treat the cause, and prevent complications. The initial priority is to establish an airway and maintain circulation (“ABCs”). This is accomplished by administering oxygen by mask or cannula; monitoring heart rate, temperature, and blood pressure; following oxygen saturation by pulse oximetry; and establishing intravenous access with administration of thiamine and a bolus of 50% glucose (glucose will terminate seizures due to hypoglycemia).

The initial anticonvulsant given is usually lorazepam delivered intravenously as soon as possible. This is soon followed by a full intravenous loading dose of fosphenytoin or phenytoin to maintain cessation of the seizures. Fosphenytoin is a water-soluble analogue of phenytoin that is converted to phenytoin in the body. Fosphenytoin can be given at a faster rate and is somewhat safer than phenytoin but is more expensive.

If fosphenytoin and lorazepam fail to control the seizures, the patient should be intubated and placed on a ventilator. Iatrogenic anesthetic coma is then induced with pentobarbital or occasionally midazolam until there is cessation of seizure activity both clinically and on the EEG. Attempts should

be made to wean these drugs slowly under EEG control to ensure that the seizures do not return.

Patients, especially children, with epilepsy who experience repeated bouts of status epilepticus can begin early treatment at home by rectal administration of a special gel formulation of diazepam. In children, this rectal delivery often stops seizures within 15 minutes.

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# 16 COMA AND CEREBRAL DEATH

## Coma

### Overview

Consciousness has 3 attributes: arousal, wakefulness, and awareness of self and environment. Arousal is the ability to awaken from sleep. This normal state is characterized by specific stages, characteristic EEG patterns, and the ability of verbal or physical stimuli to terminate sleep to wakefulness. Wakefulness and awareness are states of alertness (usually with eyes open) and characterized by appropriately creating and responding to sensation, emotion, volition, and thought. Wakefulness and awareness require the interaction of a relatively intact cerebral cortex and normally functioning reticular-activating system in the upper brainstem extending from the mid-brain to the hypothalamus and thalamus.

Loss of consciousness has several stages. *Confusion* and *delirium* are characterized by impaired capacity to think clearly and respond appropriately. In addition, delirious patients are agitated and easily distractible. These states involve a generalized disturbance of cortical function, often with EEG abnormalities. *Obtundation* is a disorder of alertness associated with slow reaction times (psychomotor retardation). Individuals can be

aroused by verbal stimuli but respond poorly to questions, with a prolonged delay in their verbal or motor responses. In *stupor* or *semicoma*, individuals require constant strong verbal or physical stimuli to remain aroused. Their responses are simple and often inaccurate. When the stimulus stops, they return to unconsciousness.

*Coma* is the pathologic state of the inability to arouse from any stimuli to produce appropriate responses. The majority of patients have impairment of reticular function. Occasionally, coma results from extensive damage to both cerebral hemispheres, but hemispheric lesions usually produce coma via transtentorial compression of the reticular formation.

### Pathophysiology

Etiologies causing coma can be divided into 3 major categories: supratentorial mass lesions, infratentorial destructive lesions, and metabolic causes. Specific causes of coma in each category are listed in Table 16-1. In the emergency room setting, the etiologies are divided about equally into drug overdoses, supratentorial or infratentorial mass lesions, and other metabolic causes.

Supratentorial structurally caused coma usually begins as a unilateral hemispheric mass that

Table 16-1 Major Causes of Coma

Supratentorial Structural (18% of Total)	Infratentorial Structural (14% of Total)	Metabolic (68% of Total)
Head Trauma <b>Contusion with brain swelling*</b> <b>Subdural/epidural hematoma</b> Intracerebral hemorrhage	<b>Brainstem/cerebellar ischemic or hemorrhagic stroke</b>	<b>Drugs</b> <b>Sedatives</b> <b>Opioids</b> Tranquilizers Salicylates
Brain Tumor	<b>Brainstem/cerebellar tumor</b>	Hypoxia Cardiac or respiratory arrest Severe anemia Toxins (carbon monoxide)
Massive Stroke Ischemic stroke <b>Cerebral hemorrhage</b>		Blood-glucose abnormalities <b>Hypoglycemia coma from excess insulin</b> <b>Hyperglycemic coma from diabetes mellitus</b>
Encephalitis		Abnormal ionic central nervous system environment Hypo/hyper blood sodium, potassium, calcium, and magnesium
Brain abscess		Organ diseases <b>Liver (hepatic coma)</b> Kidney (uremic coma) Lungs (CO <sub>2</sub> narcosis and respiratory failure) Thyroid (myxedema coma) Brain cofactor deficiency Thiamine (B <sub>1</sub> ), cyanocobalamin (B <sub>12</sub> ), and pyridoxine (B <sub>6</sub> ) deficiency Poor cerebral perfusion Hypertensive encephalopathy Obstructive hydrocephalus Bleeding with low blood volume Decreased cardiac output (myocardial infarction and cardiac arrhythmia) Toxins <b>Ethanol</b> Methanol and ethylene glycol

\* **Bold** type refers to the most-common causes within a category.

progressively expands to produce brain herniation (see Chapter 14, “Brain Tumors”). As the herniation progresses across the tentorium, the upper brainstem pushes downward, often rupturing

penetrating brainstem veins (Duret hemorrhages), producing fatal brainstem hemorrhages and ischemia. Coma from infratentorial destruction can be from ischemic brainstem stroke or a

mass (hemorrhage or tumor) involving the brainstem or cerebellum, directly damaging or compressing the reticular formation. Metabolic-caused coma primarily affects reticular formation neurons.

### Major Clinical and Laboratory Features

There are three critical questions to be answered about a comatose patient: where is the lesion? what is the cause? and is the coma stable, improving, or worsening? Generally, the physician first determines whether the etiologic category is supratentorial, infratentorial, or metabolic. The next step is

to determine the cause within the category. Obtaining a history, including drug use, from a friend or relative is extremely helpful in placing the patient into a category.

Table 16-2 gives the major clinical features found in each coma category (also refer to Figures 16-1 and 16-2). An elevated temperature and WBC count usually implies an infection (sepsis, pneumonia, or CNS), while a low temperature usually implies the patient has been comatose in a cold environment for some period of time. Rapid regular breathing often denotes a metabolic acidosis from a metabolic cause. During the physical exam-

**Table 16-2 Coma Characteristics Excluding Those Caused by Head Trauma**

Characteristic	Supratentorial Structural	Infratentorial Structural	Metabolic
Early History	Signs suggesting dysfunction of the hemisphere (hemiparesis, hemisensory defect, aphasia, and visual defect). Headaches common.	Signs of cranial nerve dysfunction. Headaches and stiff neck may be present.	Rapid onset (anoxia) or subacute progression (drugs, uremia, etc). Patient looks asleep. Headaches are uncommon. Fever may be present if sepsis or pneumonia present.
Breathing	Normal or Cheyne-Stokes sign (periodic cycles of rapid breathing followed by period of apnea).	Apneustic (deep inspiration, long pause, and prolonged exhalation at a rate of ~ 5/s) or ataxic (irregular, ineffective breathing that is often shallow).	Normal or rapid due to metabolic acidosis.
Early Eye Findings (see Figure 16-2)	Pupillary light reflexes are present but pupil size may be small or unilaterally dilated. Papilledema may be seen. Vestibuloocular reflexes may be present or impaired.	Pupil size often unequal and may be unresponsive to light (fixed). Eyes may not be parallel and vestibuloocular reflex is sluggish or absent. Papilledema is absent.	Normal size and reaction to light, normal vestibuloocular reflexes, and no papilledema.
Motor (see Figure 16-3)	Asymmetric spontaneous or pain-induced limb movements. Decorticate posturing (flexion of the arm and extension of the leg on the involved side) to pain may occur.	Bilateral limb weakness or quadraparesis may be present. Decerebrate posturing (unilateral or bilateral extension of arms and legs) to pain seen in mid-brain lesions.	Symmetric spontaneous or pain-induced limb movements.
Reflexes	Often hyperactive with Babinski sign on contralateral side.	Often normal or hyperactive. Babinski signs may appear.	Normal or depressed. No Babinski signs.
Neuroimaging	Hemispheric mass (tumor, hemorrhage, abscess, and stroke), shift of midline structures, and brain herniation. Occasional obstructive hydrocephalus.	Mass in brainstem or cerebellum and occasional cerebellar tonsillar herniation through foramen magnum.	Normal.

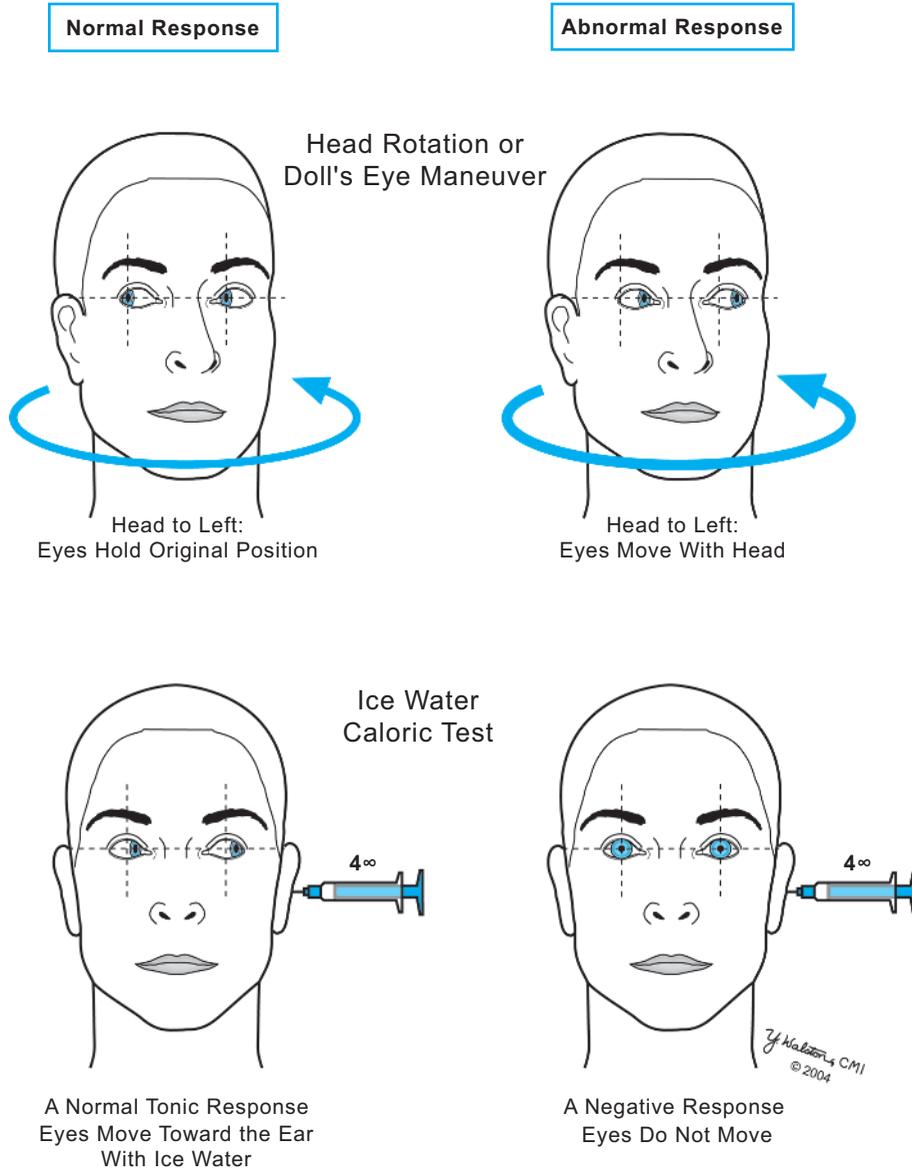
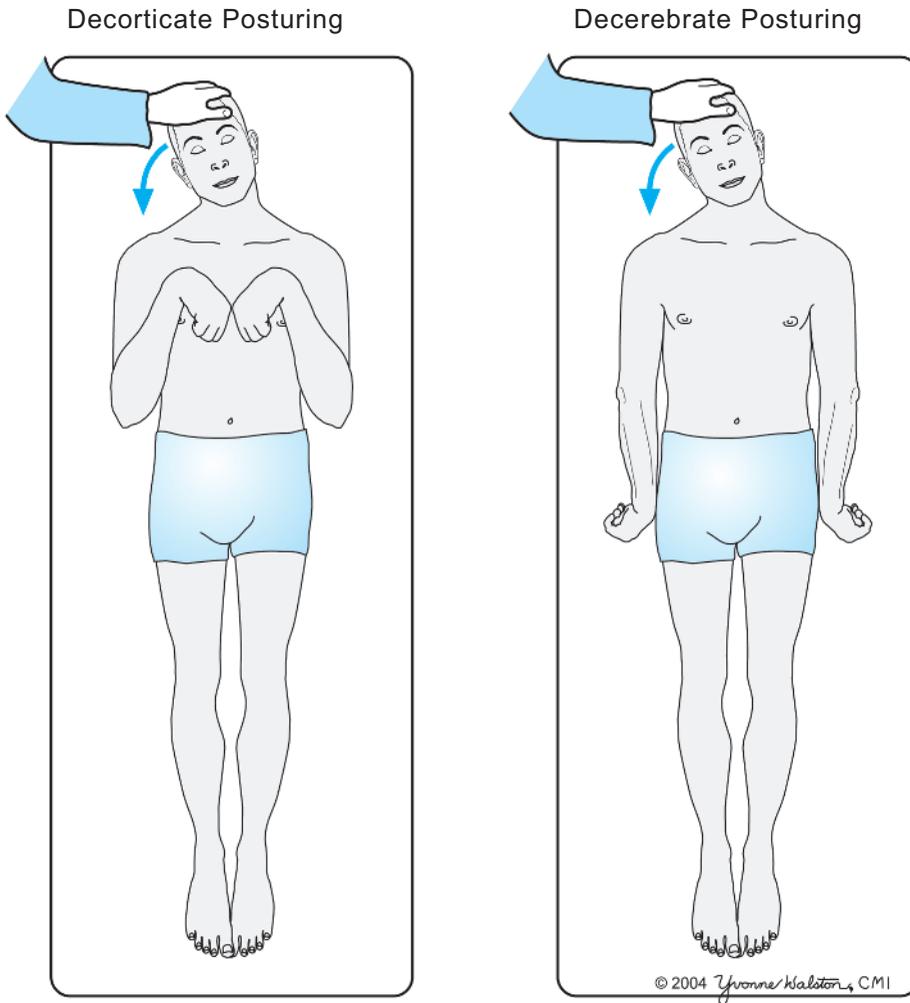


Figure 16-1 Assessment of vestibuloocular reflex in coma.

ination, attention should be paid to find signs of trauma (especially head or neck trauma), bleeding (external or internal), organ dysfunction (especially lungs, heart, kidney, and thyroid), and sepsis. Since mentation, fine sensation, and coordination cannot be tested in a comatose patient, the neurologic exam focuses on spontaneous or pain-induced limb movements, breathing patterns, ocular findings and cranial nerve function (Tables 16-2 and 16-3).

Important clues to a supratentorial location for the coma include an early history of progressive

unilateral hemispheric signs or a unilateral fixed dilated pupil. The late stages of a supratentorial coma are due to brainstem dysfunction and often appear similar to infratentorially caused coma. Infratentorial structural coma usually has a rapid onset, involves multiple cranial nerves, and produces brainstem findings before or accompanying coma. Table 16-3 lists the brainstem reflexes that can be evaluated in a comatose patient and the clues each give regarding brainstem localization. Weakness may be unilateral if the brainstem lesion



**Figure 16-2** Decorticate and decerebrate posturing reflexes. Supraorbital pressure induces posturing.

is unilateral (brainstem stroke) or bilateral if the lesion involves both halves of the brainstem (brainstem hemorrhage or tumor). Metabolic coma may have a rapid or subacute onset, usually produces mental changes before motor signs, has preserved pupillary reactions, rarely produces asymmetric motor, sensory, or reflex findings, and is often associated with systemic disease (abnormal blood findings and signs of other organ failure). Occasional patients have psychogenic coma characterized by normal muscle tone and reflexes, unpredictable vestibuloocular reflexes with the fast phase preserved on ice water caloric testing, atypical irregular breathing patterns, and nonphysiologic responses to cranial nerve testing.

### Principles of Management and Prognosis

In the emergency management of a comatose patient, the first step is control of the ABCs (airway, breathing, and circulation) (Figure 16-3). Steps include ensuring the airway is open, delivering oxygen either nasally or via intubation if needed, and establishing intravenous access. Commonly ordered tests include the following: a toxicology screen, a hemogram, electrolytes, liver-function studies, creatinine, glucose, calcium, and a “save-serum” specimen for possible future tests. Depending on the history and initial evaluation of the patient, the following drugs may be intravenously administered: thiamine, an

**Table 16-3 Bedside Examination of Cranial Nerves in a Comatose Patient**

<b>Test</b>	<b>Cranial Nerves Tested</b>	<b>Testing Method</b>	<b>Brainstem Location Tested</b>
Papillary Light Reflex	II, III	Normal: bright light shined into 1 eye causes both pupils promptly to reduce in size. Large pupil that is fixed to ipsilateral and bilateral light implies damage to CN III.	Mid-brain
Corneal Reflex	V, VII	Normal: touching cornea with cotton causes both eyelids to promptly close or blink. Failure of both eyelids to blink when stimulating 1 cornea implies dysfunction of ipsilateral CN V. Failure of 1 eyelid to blink with direct and consensual corneal stimulation implies dysfunction of ipsilateral CN VII.	Pons
Symmetrical Face Movement to Pain	VII	Normal: in light coma, ipsilateral or contralateral pain to face or body causes grimace of lower face. Unilateral grimace to stimuli implies dysfunction of CN VII.	Pons
Vestibuloocular Reflex or "Doll's Eyes" Maneuver	III, VI, VIII	Normal: when rotating head laterally, the eyes remain fixed at original target. Abnormal test result occurs when eyes move with head on lateral rotation.	Lower pons to mid-brain
Ice-Water Caloric Test	III, VI, VIII	Normal: irrigation with 25–50 mL of cold or ice water in 1 ear causes both eyes to move to side with water and stay fixed. If 1 side is absent but the opposite side normal, damage to ipsilateral CN VIII is implied. If both sides are abnormal, this implies brainstem lesion in pathways of vestibular nuclei to CN III and VI.	Lower pons to mid-brain
Gag Reflex	IX, X	Normal: suctioning of mouth or stimulation of posterior pharynx triggers gag reflex. Absent gag implies dysfunction to medullary gag center.	Medulla
Cough Reflex	IX, X	Normal: spontaneous cough or cough upon stimulating trachea. Absent cough implies dysfunction to cough center.	Medulla
Yawn or Sneeze Reflexes	V, IX, X	Presence of these long loop reflexes implies brainstem function reasonably intact.	Medulla to upper brain
Deep Tendon Reflexes	Spinal cord	Normal: limb movement in response to percussion of joint tendon. Presence implies lack of spinal shock and intact spinal cord level but does not imply brainstem or cortical function.	Spinal cord level

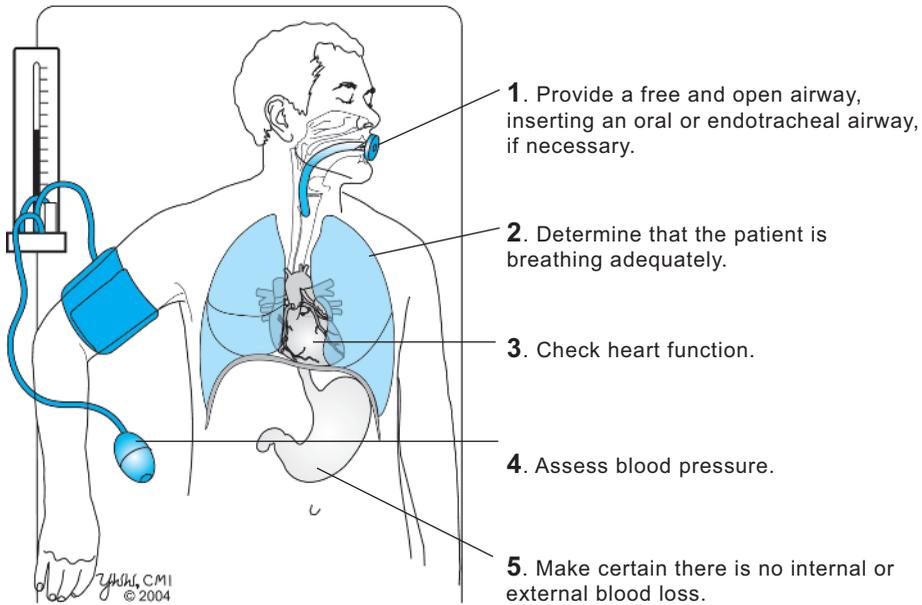
opioids antagonist, and a bolus of 50% glucose solution.

If a supratentorial cause is suspected, the situation becomes emergent and immediate cranial CT is indicated. If impending brain herniation is present, lowering of ICP is accomplished by intubation and hyperventilation (to cause cerebral vasoconstriction), administration of intravenous mannitol (to reduce cerebral fluid volume), and prompt surgical intervention (to remove a hemispheric mass or to remove CSF if obstructive hydrocephalus is present).

With infratentorial causes of coma, vital signs may rapidly worsen so intubation with mechanical ventilation and blood pressure drugs may be

needed. Neuroimaging can identify the cause, but surgical intervention is seldom indicated. If the cause of metabolic coma is due to insufficient circulation, oxygen, or glucose to the brain, rapid correction of the etiology may reverse the situation. For many other causes, including organ dysfunction and drug overdose, the patient should be stabilized, appropriate blood tests ordered to identify the etiology, and treatment focused on correcting the underlying metabolic cause.

The outcome of a comatose patient varies with the etiology but in those with a structural brain lesion the mortality is high, with severe neurologic sequelae in survivors. The following generaliza-



**Figure 16-3** Assessment of ABCs (airway, breathing, and circulation) in coma.

tions help predict outcomes from coma in patients without head trauma. Head trauma has a better prognosis (see Chapter 18, “Traumatic Brain Injury and Subdural Hematoma”):

- Coma seldom persists longer than 2 weeks. The patient dies, develops a persistent vegetative state (a chronic condition in which he or she appears awake but has no evidence of cognition), or improves, opens the eyes, and regains consciousness.
- Less than 1% of patients regain independent function if they still have absent corneal, pupillary light, or vestibuloocular reflexes after 1 day of coma.
- Only 15% of patients comatose for over 6 hours and 7% of patients comatose for 3 days recover with independent functioning.
- In metabolic coma, prognosis is best for patients with drug or endocrine causes and worst for anoxia or inadequate cerebral perfusion from any cause.

## Cerebral Death

In spite of medical advances, many comatose patients progress to death. Since these patients are often mechanically and chemically supported, it is

important to know when the brain is dead. A series of rules have been developed to diagnose brain death. Although the legal definition of brain death varies from state to state and by country, all use similar general guidelines. If the coma etiology is known and irreversible, the decision is straightforward. When the etiology is unknown, the patient must not be hypothermic (core body temperature below 30°C) or intoxicated with sedating drugs (such as barbiturates), as these conditions suppress brainstem reflex function, giving the false impression of death. In patients with body temperatures below 30°C or with high levels of barbiturates, brainstem reflexes may disappear. The coma should have persisted for at least 6 to 12 hours. In children, an initial exam usually is followed by a confirmatory exam up to 24 hours later. In adults the confirmatory exam is often optional. Table 16-4 lists the neurologic criteria that must be met. The presence of deep tendon reflexes implies only spinal cord segmental function, which will soon disappear and does not negate a diagnosis of brain death.

A series of confirmatory tests are available to establish brain death. These tests are optional in adults and seldom performed when the etiology is known. In infants, however, confirmatory tests are recommended. The most common test is an EEG, which demonstrates isoelectric silence (no detec-

**Table 16-4 Common Clinical Criteria for Brain Death**

• Coma, usually for $\geq 6$ hours
• Absence of marked hypothermia ( $<30^{\circ}\text{C}$ ) or sedative intoxication
• Absence of motor responses
• Absence of brainstem reflexes (see Table 16-3)
• Absence of respiratory drive (at a $\text{PaCO}_2$ that is 60 mm Hg or 20 mm Hg above baseline values)

tion of cerebral electrical activity when the EEG machine is at maximum sensitivity). When neurons and glia die, the cells swell (cytotoxic edema), increasing ICP and preventing cerebral arterial blood flow. Tests such as a cerebral arteriogram, transcranial Doppler ultrasonography, or SPECT blood flow study can be done to prove absence of cerebral blood flow.

When the legal criteria for brain death are met, life support can be discontinued and if other criteria are met, organs can be harvested for donation to others.

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# 17 DISORDERS OF THE DEVELOPING NERVOUS SYSTEM

## Overview

Amazing events in growth and development occur before birth as one cell develops into an infant. In spite of the immense complexity, most infants are born with a normal nervous system containing 50 to 100 billion functioning nerve cells. Unfortunately, 1% to 2% of infants are born with neurodevelopmental defects. About 40% of deaths in the first year of life are related to malformations of the CNS and an unknown percent of spontaneous deaths in utero result from CNS maldevelopment. Although the cause of neurodevelopmental defects is unknown in 60%, defects can occur from several causes, including genetic mutations, exposure to toxins or teratogens, CNS infections, metabolic deficiencies, and trauma. Table 17-1 lists some of the more commonly recognized causes.

Equally important as the cause of the CNS insult is the timing. By 3 weeks' gestation, the primitive neural tube has begun to develop and CNS growth and maturation continue throughout the embryonic period (0–8 weeks), the fetal period (9–38 weeks), infancy, and well into late childhood. The characteristics of the malformation depend on the timing of the CNS developmental disruption, although some insults, such as genetic mutations, may disrupt development over extended periods,

causing a variety of defects. In addition, multiple abnormalities may occur from a single primary deficit in early morphogenesis, causing a cascading process of secondary and tertiary errors in morphogenesis. Insults that affect the CNS from weeks 3 to 6 usually produce major morphologic abnormalities while insults occurring later may produce more subtle or localized dysfunction. Thus it is possible to determine the latest time in gestation a malformation could occur but not the earliest. Table 17-2 presents the gestational timing of some neurodevelopmental milestones.

Based on a limited number of fetuses studied by anatomists and experimental studies of vertebrates and invertebrates, we are gaining a glimpse of the incredibly complex sequence of events that must occur at precise times for normal brain development. The basic steps of development are neurulation, neuronal and glial proliferation, migration, differentiation of neurons with axonal, dendritic, and synaptic development, programmed cell death, and myelination.

In neurulation, primitive cells destined to become neurons originate close to the neuroepithelium of the neural tube. These cells begin rapidly replicating by the fourth week, producing cells that differentiate into bipolar neuroblasts. Some radial glia appear early and serve as scaffolding for

**Table 17-1 Major Recognized Causes of Neurodevelopmental Defects of the Nervous System**

<b>Genetic Mutations</b>
Mutations primarily affecting gray matter (neurons) Tay-Sachs disease
Mutations primarily affecting white matter (myelin and their cells of origin) Adrenoleukodystrophy Krabbe disease
Unbalanced chromosomes (from duplications or deletions) Down syndrome Fragile X syndrome
<b>Toxins</b>
Alcohol Organic mercury Lead
<b>Teratogenic Drugs</b>
Anticonvulsants (phenytoin, carbamazepine, and valproic acid) Thalidomide
<b>Congenital Infections</b>
Rubella Cytomegalovirus Toxoplasmosis Syphilis
<b>Metabolic Diseases</b>
Phenylketonuria
<b>Ionizing Radiation</b>
Defects uncommon unless radiation exposure is very high, which causes fetal death

neurons to migrate to the marginal layer, which will become the gray matter of the cerebral cortex. Ultimately the radial glia divide and become astrocytes. The migration of these postmitotic neurons occurs in a precise orderly manner that is largely completed by the end of the fifth month but does continue at a slow rate until birth. This process appears to produce an excess number of neurons

that are subsequently pruned to the appropriate number by a process of programmed cell death called *apoptosis*. Somehow neurons that do not establish correct neuronal connections by late pregnancy are triggered to die. Apoptosis does not elicit inflammation or gliosis, so there is no histologic evidence of their premature death.

Few fetal genes that control this intricate process have been characterized. Homeobox genes comprise a family of genes that encode DNA-binding proteins that regulate gene expression and control various aspects of morphogenesis and cell differentiation. Mutations in homeobox genes often produce malformations in the brain and other organs.

Many terms describe abnormal brain tissue. The term *dysplasia* refers to abnormal cellular organization resulting in structural and functional consequences. Dysplasias may be localized (such as a hemangioma) or generalized, affecting a variety of structures from widespread distribution of the tissue defect. *Heterotopias* are portions of an organ displaced to an abnormal site within the same organ of origin, such as nodules of gray matter located in deep white matter due to incomplete neuronal migration. A *hamartoma* is a portion of tissue at the proper site but is architecturally disorganized, such as a focus of abnormal cortical lamination due to disorganization of pyramidal neurons. *Malformation* refers to a structural defect arising from a localized error in morphogenesis and may contain one or more of the features described above. *Deformation* occurs when normally formed tissue is secondarily damaged.

## Anencephaly

### Introduction

Anencephaly is an abnormality of neurulation that occurs because of failure of closure of the anterior end of the neural tube. The timing of the insult therefore occurs around week 4 of gestation.

### Pathophysiology

The causes are unknown. The incidence of anencephaly in the United States is 1/1,000 live births. Failure of anterior neuropore closure results in failure of development of the forebrain and calvarium.

**Table 17-2 Milestones in Pre- and Perinatal Development**

<b>Time Period of Gestation</b>	<b>Major Developmental Event</b>
<b>Week(s)</b>	
3	Neural tube invaginates
4	Anterior, then posterior ends of neural tube close Brain and head represent 50% of total body length Rapid neuronal division into bipolar neuroblasts at rates up to 250,000 divisions/min Radial glia appear and migration begins
5	Lens placodes of eye develop Forebrain, midbrain, and hindbrain become evident Neuronal migration largely complete Dorsal and ventral horns of spinal cord appear Peripheral nerves appear
6–8	Migration of neurons Ears develop Limbs develop All major organs under development
9–12	Gross brain structure established Glial development and migration appears Very rapid growth of axons and synapses Muscle contractions begin
13–20	Rapid brain growth Central nervous system (CNS) myelination begins $\alpha$ -fetoprotein elevates in amniotic fluid and maternal serum if there is failure of proper neural tube closure
21–40	Primary cerebral fissures appear followed by secondary cerebral sulci Myelination continues Synaptic development continues Neuronal pruning of excess neurons by programmed apoptosis
Birth	Head is 25% of total body length Peripheral nerve myelination almost complete but CNS myelination continues through age 2 years Cry vigorous, sucks and swallows liquids, yawns Suck, root, grasp, and Moro reflex present Head control present Visual and auditory responses elicitable
<b>Months</b>	
2–5	Rapid brain growth continues with head circumference growing at 2 cm/month in first 3 mo and 1 cm/mo during months 4–6 Neurons develop more complex dendrites and synapses Oligodendrocytes and astrocytes in matrix zones continue to divide and migrate to about 6 months Voluntary or social smile appears Head control improves Eye contact increases Turns to sounds
6–11	Rolls over, crawls, begins sitting Babbles, recognizes parents, says “Ma Ma” Head circumference grows at $1/2$ cm/mo Moro response and grasp reflex disappear
12	Neuronal dendrites continue growth but head circumference growth slows to $1/4$ cm/mo Walks with hand held Uses pincer grip of thumb and forefinger Single words appear Babinski sign disappears

(Table continues)

Table 17-2 (Continued)

Time Period	Major Developmental Event
<b>Months</b>	
15	Walks independently Follows simple commands
18	Runs stiffly Knows about 10 words, identifies pictures Feeds self
24	Runs well, climbs stairs one step at time, opens doors Puts 3 words together (subject, verb, object) Tells of immediate experiences

### Major Clinical Features

The most common phenotype has a lack of the cerebral cortex and variable loss of the basal ganglia and upper midbrain, leaving in its place a small hemorrhagic, fibrotic mass of degenerating glia and neurons. The frontal, parietal, and occipital bones are absent, leaving an open calvarium above the eyes.

### Major Laboratory Findings

Polyhydramnios (excess amniotic fluid) is a frequent feature. Sonograms are abnormal and demonstrate the malformed head. There is marked elevation of serum and amniotic  $\alpha$ -fetoprotein, which is synthesized by the fetal liver, circulates in fetal blood, and is excreted in fetal urine into the amniotic fluid. It is then swallowed and digested by the fetal GI tract. Thus, amniotic fluid and maternal blood normally contain little  $\alpha$ -fetoprotein. The protein is elevated in fetal conditions such as open neural tube malformations, abnormalities in the upper GI tract, multiple fetuses, and fetal death. The optimal time to test amniotic fluid for  $\alpha$ -fetoprotein is during weeks 14 to 16 gestation, while maternal serum testing occurs at 16 to 18 weeks; both are nearly 100% elevated in anencephaly.

### Principles of Management and Prognosis

About three-quarters of affected infants are dead at delivery and the others die in the neonatal period. However, living infants often make sucking and chewing movements and have simple limb

movements demonstrating that lower brainstem, spinal cord, and motor neurons are functioning.

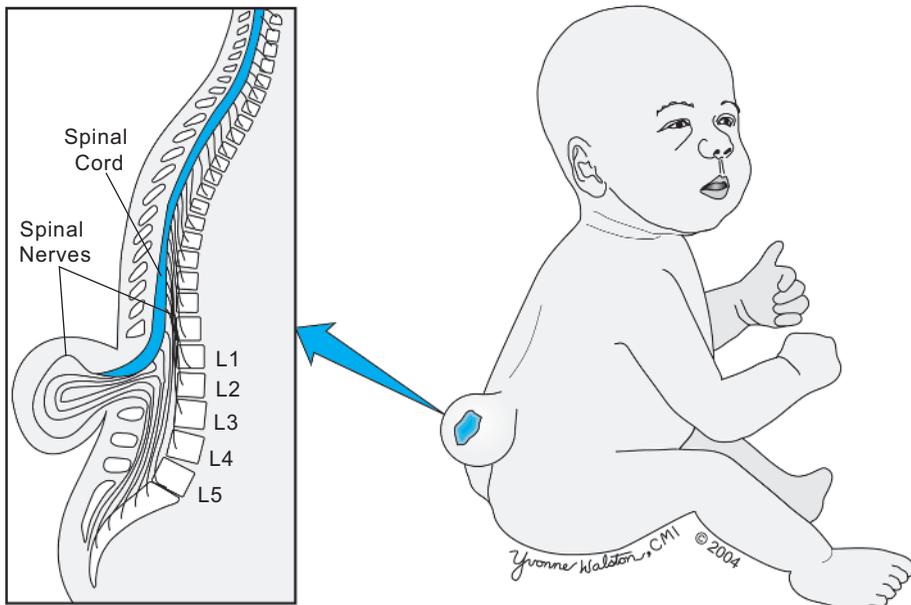
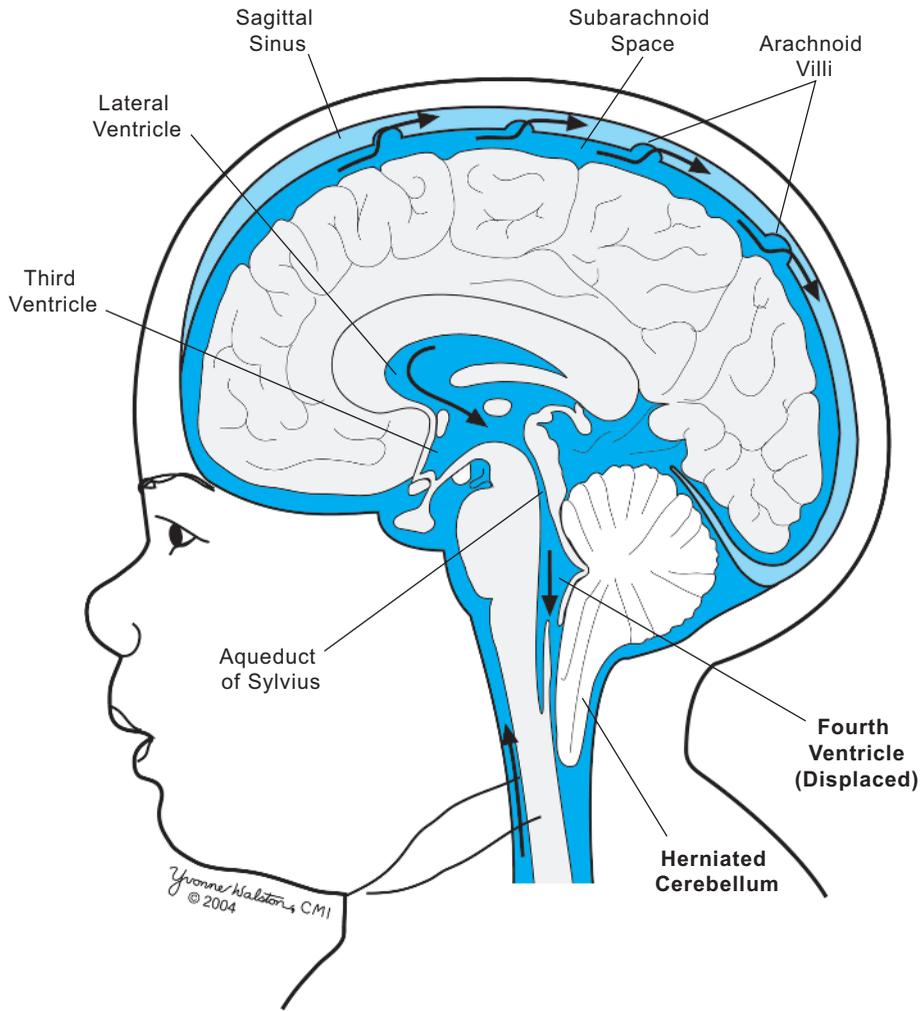
## Chiari Type I and II Malformations

### Introduction

Chiari type I and II malformations are dysplasias of the brainstem, cerebellum, and spinal cord. The etiology is unknown, but there is suspicion of a homeobox gene abnormality. Patients with Chiari type I malformation often have a variable amount of downward displacement of the cerebellar tonsils, which is often found incidentally by neuroimaging. Some individuals develop clinical signs at adolescence when they develop headaches from progressing hydrocephalus, limb spasticity, cerebellar ataxia, and lower cranial nerve dysfunction.

### Pathophysiology

The key anatomic features of Chiari II malformation consist of (1) downward displacement and extension of the cerebellar vermis through the foramen magnum and into the cervical canal and (2) downward displacement of the ventral medulla and the inferior fourth ventricle into the cervical canal (Figure 17-1a). In addition, the following associated features frequently occur: (1) elongation of the upper medulla and pons, (2) narrowing of the aqueduct of Sylvius, (3) fibrosis of the cerebellar CSF exits of the fourth ventricle (foramens of Luschka and Magendie), and (4) hydrocephalus



**Figure 17-1** Chiari II malformation. (a) Cerebellar and medullary downward displacement. (b) Meningomyelocele.

secondary to features 2 and 3, and (5) an associated meningocele in the lumbosacral area. In a meningocele, failure of the lower vertebral arches to close causes extrusion of the dura, arachnoid and cauda equina, or spinal cord into a cystic swelling that protrudes the skin above the lower back (Figure 17-1b).

### Major Clinical Features

The typical child with Chiari type II malformation has progressive hydrocephalus, variable cerebellar ataxia, and lower CN VI though XII dysfunction, with horizontal diplopia, facial weakness, deafness, sternomastoid muscle weakness and head lag, laryngeal stridor, and tongue atrophy. There is variable spastic paraparesis in the arms from secondary cervical stenosis and cervical myelopathy. The meningocele causes variable paralysis and atrophy of lower-leg and buttock muscles, loss of bowel and bladder control, and lumbar kyphosis. Cysts may develop in the cervical spinal cord, producing syringomyelia with variable loss of sensation (especially pain and temperature) and atrophy of arm muscles.

### Major Laboratory Findings

The diagnosis of Chiari II is confirmed in infants born with a meningocele by MRI, demonstrating the anatomic abnormalities, including protrusion of the cerebellar vermis below the foramen magnum.

### Principles of Management and Prognosis

Treatment of infants with type II defects usually involves placement of a ventriculoperitoneal shunt to relieve the increased ventricular CSF pressure from obstructive hydrocephalus and creating a new pathway for exit of ventricular CSF. Depending upon the extent of the lumbosacral nerve damage as the child grows older, bracing may be needed for walking and surgical placement of rods along the lower vertebral bodies for stability to correct the secondary kyphosis that develops. Urinary tract infections are common and secondary kidney problems may develop. While many children with Chiari II malformation have mental retardation, many do not and grow to adults who live normal

productive lives. Most children with Chiari I malformation have normal intelligence.

The incidence of both neural tube defects such as anencephaly and Chiari malformations have been greatly reduced by the use of supplemental folate, best administered before conception.

## Phenylketonuria (PKU); Phenylalanine Hydroxylase [PAH] Deficiency)

### Introduction

Metabolic disorders include derangements in metabolism of amino and organic acids. This includes storage diseases, mitochondrial enzyme defects, and leukodystrophies. These infants usually appear normal at birth but subsequently develop cerebral abnormalities. PKU is the most common disorder of amino acid metabolism and has an incidence in the United States of 1/14,000 births. PAH deficiency is an autosomal recessive disorder that results in intolerance to the dietary intake of the essential amino acid phenylalanine and produces PKU children with profound and irreversible mental retardation when not treated. PKU is caused by mutations in the *PAH* gene on chromosome 12q23.2. Some mutations allow for partial PAH enzyme function and produce milder forms of the disease.

### Pathophysiology

Phenylalanine is metabolized primarily in the liver by hydroxylation via PAH to tyrosine. Mutations of the PAH enzyme cause abnormal elevations in plasma phenylalanine and low tyrosine levels. Normal plasma phenylalanine levels are <120  $\mu\text{mol/L}$ ; affected infants are born with normal levels unless the mother has PKU not controlled by diet. After birth, dietary exposure occurs with consumption of either mother's or cow's milk that is rich in phenylalanine and cannot be metabolized to tyrosine. When plasma phenylalanine levels rise above 1,000  $\mu\text{mol/L}$ , damage to the developing CNS occurs. Up to 1 g/d of excess phenylalanine and phenylpyruvic acid is then excreted in urine.

Studies suggest that elevated brain-free phenylalanine and decreased levels of large neutral amino acids (tyrosine and methionine) cause

decreased protein synthesis, increased myelin turnover, and abnormalities in dopamine and norepinephrine neurotransmitter systems. The cerebral cortex that was histologically normal at birth develops abnormalities of myelination, dendritic growth, and synaptic development—i.e., systems that normally continue to mature after birth are affected. In occasional untreated infants, degeneration of established white matter may develop.

### Major Clinical Features

Clinically, infants are normal at birth. Over the first year of life, they develop eczematous skin rashes, progressive mental retardation, microcephaly, seizures, and behavioral problems. Hypopigmentation of hair, skin, and iris occurs due to inhibition of tyrosinase and lack of melanin production. Excretion of excessive phenylalanine and its metabolites creates a musty body odor. If PKU is not treated early, the mental retardation is irreversible. Untreated older children may develop spasticity, hyperactive reflexes, and paraplegia. There is increasing evidence that affected infants treated with careful phenylalanine-deficient diets grow to adulthood with an IQ in the broad range of normal. However, subtle cognitive deficits are present. Children experience delayed acquisition of speech, have more behavioral problems, and have some impairment of executive function on neuropsychologic tests. Affected siblings have a lower IQ than those unaffected. Adults who go on a regular diet also may develop mild spasticity and subtle cognitive deficits.

### Major Laboratory Findings

The diagnosis is made by newborn screening in virtually 100% of cases, based upon the detection of hyperphenylalaninemia (levels  $>1,000$   $\mu\text{mol/L}$ ) using the Guthrie (microbial assay) test on a blood spot obtain from a heel prick obtained several days after feeding begins. The Guthrie screening test usually is confirmed by more specific methods such as tandem mass spectrometry. Molecular genetic testing of the *PAH* gene exists but is difficult and expensive since many possible mutation sites exist.

Neuroimaging is normal at birth and later detects irreversible abnormalities mainly in white matter. Histologic changes in untreated cases

include hypomyelination or demyelination of white matter, gliosis, and widespread neuronal loss with gross microcephaly.

### Principles of Management and Prognosis

The goal of treatment is normalization of plasma concentrations of phenylalanine and tyrosine and the prevention of cognitive disorders. A diet restricted in phenylalanine should be instituted as soon as possible and continued at least into adolescence, and in severe cases for life. A phenylalanine-free medical formula with supplemental tetrahydrobiopterine is needed along with protein restriction, as protein restriction only is insufficient to provide sufficient nutrition and maintain plasma phenylalanine levels  $<300$   $\mu\text{mol/L}$  (5 mg/dL). How high plasma phenylalanine levels can rise in adulthood before cognitive impairment occurs is unclear. However, noncompliance with dietary restrictions and markedly elevated plasma phenylalanine levels can result in decreased cognitive functioning and white matter abnormalities detectable on MRI. Plasma phenylalanine levels must be monitored closely and maintained below 300  $\mu\text{mol/L}$  during pregnancy, as high maternal phenylalanine levels can produce fetal abnormalities.

## Tay-Sachs Disease (Hexosaminidase A Deficiency)

### Introduction

Tay-Sachs disease is the classic example of a lipid-storage disease and of a genetic disease that primarily affects gray matter (neurons of the brain and retina). Clinicians often divide degenerative diseases in infants and children into those primarily affecting gray or white matter (Table 17-3).

Tay-Sachs disease is a fatal autosomal recessive infantile disease due to severe deficiency of  $\beta$ -hexosaminidase A enzyme, resulting in abnormal accumulation of glycosphingolipid GM2 gangliosides within neurons, leading ultimately to neuronal death. Although cases have been reported in all ethnic groups, the incidence is markedly higher in Jewish communities of Central and Eastern European descent (Ashkenazi Jews). Before current genetic testing, the incidence of Tay-Sachs disease in this population was 1/3,600 births. The

**Table 17-3 Clinical Features of Diseases Affecting Primarily Gray and White Matter**

<b>Gray Matter (Neurons of Brain and Retina)</b>	<b>White Matter (Myelin and Axons)</b>
Loss of previously attained intellectual skills	Spasticity  Sensory abnormalities
Seizures	Ataxia and incoordination
Aphasia	Visual field defects
Loss of visual acuity	Visual loss
Memory loss	
Variable muscle atrophy from loss of anterior horn neurons	

incidence in other populations is at least 10-fold lower.

### Pathophysiology

Hexosaminidase A and B are two catabolic enzymes that hydrolyze gangliosides with terminal  $\beta$ -N-acetylgalactosamine residues. In Tay-Sachs disease, there is a mutation in the hexosaminidase- $\alpha$  subunit such that the enzymatic activity of hexosaminidase B is normal but is nearly absent in hexosaminidase A. As a consequence, the ganglioside GM2 cannot be catabolized and accumulates within the cytoplasm of neurons, eventually causing the neuron's death. In the retina, the fovea lacks ganglion cell bodies. Thus accumulation of whitish GM2 gangliosides in ganglion neurons surrounding the fovea is seen with an ophthalmoscope as a "cherry red spot."

Pathologically, there is a large brain containing excessive neuronal glycolipids (up to 12% of the brain dry weight contains GM2 gangliosides). There is widespread loss of neurons, with reactive gliosis. All remaining neurons are distended with glycolipid.

### Major Clinical Features

Affected infants appear normal at birth. By 3 months, infants develop mild weakness, myoclonic

jerks, and startle responses to sudden noises. By 9 months, the infant fails to achieve milestones and is losing those already acquired. Weakness is more pronounced. There is diminished visual attentiveness from loss of acuity, and a "cherry red spot" is seen in the retina on funduscopy. By 12 months, voluntary limb movements are minimal, vision is lost, and partial complex and absence seizures develop. By year 2, the infant has decerebrate posturing, marked seizures, swallowing difficulties, and becomes almost vegetative. Death from bronchopneumonia occurs between ages 2 and 4 years.

### Major Laboratory Findings

The diagnosis is established by demonstration of deficient hexosaminidase A enzymatic activity in the serum or WBCs of a symptomatic individual in the presence of normal activity of the hexosaminidase B isoenzyme. Mutation analysis of the *HEXA* gene on chromosome 15q23-q24 can be done, but is less sensitive than the enzymatic assay because current assays do not detect all 90 known mutations.

Neuroimaging shows an enlarged head from gliosis and not hydrocephalus. The EEG is abnormal early and shows paroxysmal slow waves and spikes.

### Principles of Management and Prognosis

No treatment currently exists to replace the missing hexosaminidase A enzyme, and the disease relentlessly progresses to death. The goal of management is to provide supportive care, give adequate nutrition and hydration, minimize respiratory infections, and control seizures with anticonvulsants.

Since asymptomatic, heterozygote carriers can be detected by a simple, inexpensive, and sensitive serum hexosaminidase A enzyme assay, genetic screening as well as prenatal genetic tests are frequently done. Currently, Jews of Ashkenazi extractions are often tested when reaching adulthood. Prenatal testing is available when both parents are heterozygous or the mother is heterozygous and the father is unknown. The hexosaminidase A assay can be performed upon a chorionic villus sample at 10 to 12 weeks' gestation or by amniocentesis at 16 to 18 weeks' gestation.

## Down Syndrome

### Introduction

Chromosomal abnormalities occur when there are too many copies, too few copies, or abnormal arrangements (duplications or deletions) of normal genes. At least 0.5% of all live births and 50% of spontaneously aborted fetuses in the first trimester are the consequence of chromosomal imbalances. The human genome contains approximately  $6 \times 10^9$  base pairs of DNA, and is 2 m long if uncoiled. Each somatic cell has 22 pairs of homologous chromosomes that are identical in morphology and constituent gene loci plus 1 pair of sex chromosomes. Malformations are likely to develop if this genetic arrangement is significantly altered.

Most chromosomal disorders involving autosomal chromosomes are associated with multiple congenital abnormalities. Many of these individuals have in common some degree of intrauterine and postnatal microcephaly, mental retardation, seizures, and assorted ocular, gastrointestinal, and skin abnormalities. Only 3 autosomal trisomies (13, 18, and 21) survive to term and only trisomy 21 or Down syndrome survives past one year. Some patients with various chromosome deletions express only mild signs.

Down syndrome occurs around the world and has a prevalence of 90/100,000 live births and increases dramatically with maternal age >35 years.

### Pathophysiology

About 95% of individuals with Down syndrome have trisomy 21 or three copies of chromosome 21 from nondisjunction mainly during gamete formation in the mother. The risk of this maternal abnormality increases with age. Of these cases 5% have translocations where all or part of chromosome 21 is attached to another chromosome, usually 14. It is still unknown how the presence of additional chromosome 21 genes causes this complex but easily recognized syndrome. Chromosome 21 is the shortest chromosome, and genetic mapping of the human chromosome suggests it contains only 225 genes. Clinical features are identical in children with trisomy or translocation.

Brain size and weight are normal at birth, but there is foreshortening of the anterior–posterior head diameter, flattening of the occiput, and nar-

rowing of the superior temporal gyrus. The primary gyri are wider than normal and secondary gyri are narrower. The cerebellum and brainstem are smaller than normal. Reduced numbers of neurons in the cortex and hypomyelination are present and continue in subsequent growth. As the child grows older, there is significant reduction in linear growth and brain growth. Most adults have short stature and mild microcephaly.

Adults demonstrate basal ganglia calcifications and after the age of 30 years develop senile plaques and neurofibrillary tangles similar to those seen in Alzheimer's disease. By age 50 years, there is considerable loss of cortical neurons and brain atrophy.

### Major Clinical Features

Newborns have hypotonia, hyperextensible joints, excess skin on the back of the neck, flat facial profiles, slanted palpebral fissures, overfolded helices, protruding tongues, short fifth fingers, and single palmar creases (Figure 17-2). Congenital heart disease is present in 50%. Moderate mental retardation becomes apparent as the child grows. In addition, the child may develop strabismus, nystagmus, small genitalia, and pectus excavatum. Some children have immunoglobulin imbalance and a susceptibility to respiratory infections while some, especially older children, develop hypothyroidism. Most males are infertile. In adulthood after the age of 30 years, a progressive dementia that has features of Alzheimer's disease often worsens the existing mental retardation.

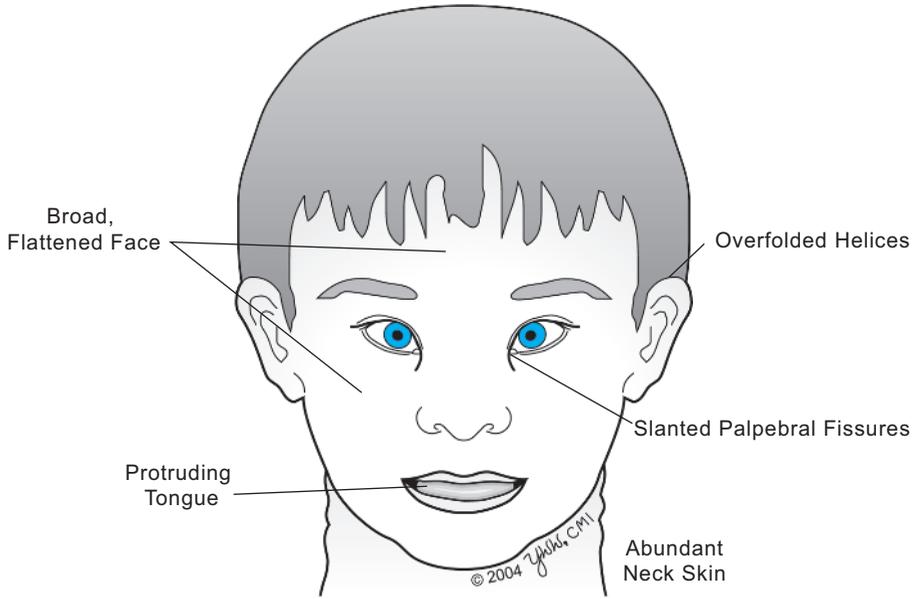
### Major Laboratory Findings

Neuroimaging in childhood may demonstrate hypomyelination for age. In adults, basal ganglia calcifications are seen in 50% of cases; brain atrophy is seen in older adults.

Karyotyping performed on blood lymphocytes or skin fibroblasts establishes the diagnosis and determines whether the cause is trisomy 21 or translocation. Finding a translocation means that subsequent children of the mother or affected individual carry a 50% risk of having Down syndrome.

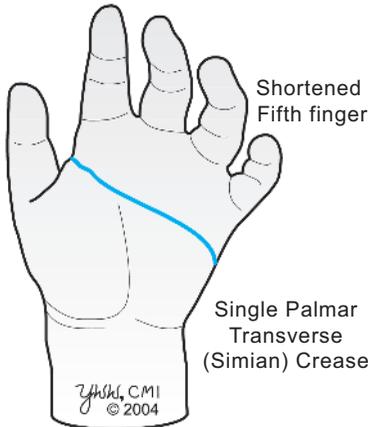
### Principles of Management and Prognosis

The goal of management is to prevent or minimize recognized malformations of the heart, thyroid,

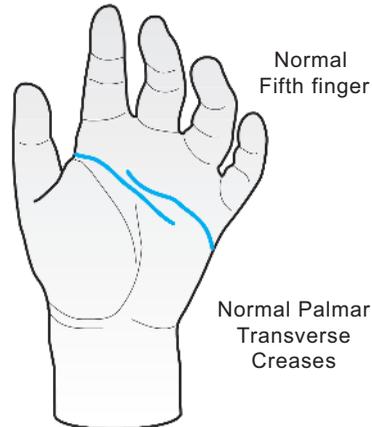


### Down Hand

Broad



### Normal Hand



**Figure 17-2** Down syndrome (Trisomy 21) features.

and GI tract and maximize the potential of the individual. Infants should have careful cardiac, hearing, and thyroid evaluations. Respiratory and ear infections should be treated aggressively. Older children may require special school supports but should attend regular elementary and high schools. Repeat testing in children and adults for problems of thyroid function, vision, hearing, and cardiac problems should be done. The mean age of survival at birth is 50 years.

## RECOMMENDED READING

Fenichel GM. *Clinical Pediatric Neurology: A Sign and Symptom Approach*. 4th ed. Philadelphia: W.B. Saunders Company; 2001. (*This and other pediatric neurology textbooks cover the many disorders of the developing nervous system in detail.*)  
 Hoffman HJ, Hendrick EB, Humphreys RP. Manifestations and management of Arnold-Chiari malformations in patients with myelomeningo-

cele. *Childs Brain* 1975;1:255–259. (Old but good review.)

Medical Research Council Working Party on Phenylketonuria. Phenylketonuria due to phenylalanine hydroxylase deficiency: an unfolding story. *BMJ* 1993;306:115–119. (Excellent review of subtle cognitive and neurologic

changes that develop in children treated with strict phenylalanine diets.)

Ryan S, Scriver CR. Phenylalanine hydroxylase deficiency. Available at: <http://www.geneclinics.org>. Accessed August 26, 2002. (This Web site has outstanding, constantly updated reviews on many genetic diseases.)

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# 18 TRAUMATIC BRAIN INJURY AND SUBDURAL HEMATOMA

## Traumatic Brain Injury

### Overview

Traumatic brain injury (TBI) is the most common cause of death and disability in young adults. Each year in the United States, almost 2 million people sustain TBI, 1 million receive emergency room or outpatient care, and 270,000 require hospitalization. The incidence of TBI is 200/1,000,000 individuals. Nearly 50,000 people die each year and 80,000 have severe neurologic disabilities from TBI.

Young adult males are at highest risk for TBI, but the syndrome occurs at all ages, including babies (shaken baby syndrome). In young adults, motor vehicle accidents are the leading cause while in older adults, falls prevail.

TBI is graded as mild, moderate, and severe based on the Glasgow coma scale (GCS) after resuscitation (Table 18-1). The GCS is easily administered and helps in acute management and prognosis of the patient. The scale is based on responses to eye opening, limb movements, and verbalization, with a score of 15 being normal. GCS scores rank the degree of injury as

Table 18-1 Glasgow Coma Scale

Eye Opening		Motor Response		Verbal Response	
Response	Score	Response	Score	Response	Score
Spontaneous	4	Obeys	6	Oriented	5
To speech	3	Localizes	5	Confused	4
To pain	2	Withdraws	4	Inappropriate	3
None	1	Abnormal flexion (decorticate rigidity)	3	Incomprehensible	2
		Extension response (decerebrate rigidity)	2	None	1
		None	1		

mild (13–15), moderate (9–12), and severe (3–8).

### Pathophysiology

Brain damage from TBI in nonmissile head injury is divided into 2 mechanisms: primary and secondary brain injury. Primary injury occurs at the moment of head trauma, with several factors contributing to the brain damage. Skull fractures portend considerable brain injury and are found in 3% of head trauma patients seen in emergency rooms but are present in over 50% of patients hospitalized and 80% of those who die. Over 1/2 of patients have a linear fracture of the skull vault; 4% of these fractures are depressed from their normal location.

The piaarachoid membrane remains intact over a contusion, but in a brain laceration, it tears, producing bleeding. Contusions and lacerations characteristically occur on the inferior surfaces of the frontal and temporal lobe poles where the brain comes in contact with bony protuberances of the skull base. The crests of the gyri incur the greatest injury, but the damage may penetrate to varying depths. Contusions may develop at the site of injury (coup) or to the brain diametrically opposite the site of injury (countercoup).

Diffuse axonal injury may be seen in over 1/2 of TBI patients when unconsciousness lasts as short as 5 minutes. The majority of axonal injury occurs from tearing the axon in the white matter at the moment of impact, but some axonal destruction develops later when excess calcium entry and swelling further damage axon segments (Figure 18-1). Common sites of axonal injury include cerebral gray and white matter, corpus callosum, cerebellum, and brainstem. Initially, an axon bulb (retraction bulb) develops, followed in a few weeks by accumulation of microglia at the injury site. Months later, wallerian degeneration of the axon tract occurs.

Diffuse vascular injury is commonly seen in severe TBI. Petechial hemorrhages are seen throughout the hemispheres, basal ganglia, and brainstem from shearing damage to small blood vessels. Intracerebral hematomas develop in 10% to 15% of patients, may be single or multiple, and are often located in the frontal and temporal lobes.

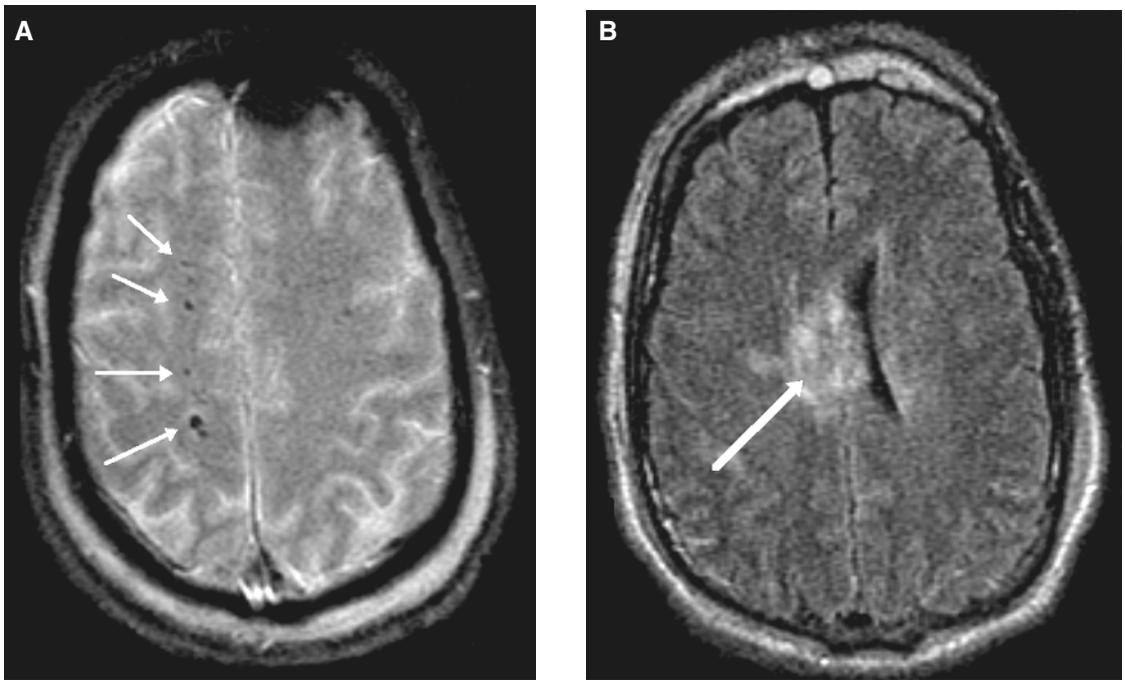
Secondary injury is a multifactorial process that initiates at the moment of injury but does not

present clinically until later. Brain swelling, the most important cause of secondary injury, begins shortly after the TBI. Local edema can be found at areas of brain necrosis as a result of contusion, expanding intracerebral hematomas, or pockets of subarachnoid blood. Diffuse brain swelling results from brain hypoxia and ischemia that open the blood–brain barrier and allow egress of plasma into the brain (cerebral edema). As the ICP elevates, further brain ischemia may develop if the cerebral blood flow falls to critical levels and no longer perfuses brain tissue. Subdural or epidural hematomas may also contribute to increasing ICP. Once ICP reaches a critical level (above 20–25 mm Hg), ischemic brain damage develops. One study found ischemic brain damage present in 90% of TBI patients (severe in 27%, moderate in 43%, and mild in 30%). The most-common locations of ischemic damage were the hippocampus, basal ganglia, and cerebral hemispheres in the watershed territories (boundary zones between the anterior and middle cerebral arteries and middle and posterior cerebral arteries). Neuronal death, particularly in the hippocampus, may be mediated by the release of glutamate. This activates adjacent NMDA receptors in calcium channels. Calcium influx then leads to cell death.

### Major Clinical Features

Many patients with TBI also have severe injuries to other body parts; these will need to be identified and treated. This section discusses only the brain signs and symptoms seen in TBI.

Information about the cause of head trauma, location of head impact, and duration of unconsciousness should be obtained from witnesses. Focal blows from blunt trauma are more likely to cause skull fractures and contusions while high-velocity accidents and falls often produce more diffuse axonal injury. The head should be examined for signs of penetrating injuries. Signs suggestive of a basal skull fracture include periorbital ecchymoses or “racoon eyes,” CSF drainage from the nose (rhinorrhea), bleeding from the external auditory canal, or ecchymoses over the mastoid bone (Battle’s sign). Pupils should be examined for symmetry in size and function. A unilateral fixed dilated pupil suggests brain uncal herniation, unless there has been direct eye trauma.



**Figure 18-1** (A) MRI of diffuse brain injury 5 days after a high-speed bicycle accident. Arrows indicate several small areas of subcortical hemorrhage (dark areas in the right hemisphere). (B) FLAIR MRI image of the same patient showing edema and blood in the posterior body of the corpus callosum. (Courtesy of Blaine Hart, MD)

Mild TBI (GCS scores 13–15) is the most common. These patients often do not lose consciousness but are stunned (“see stars”) or experience a simple concussion (brief loss of consciousness without permanent brain damage). They may not recall the event. Such patients may experience short-term memory and concentration difficulties that persist for days to months. Some complain of posttraumatic symptoms such as headaches, giddiness, fatigability, insomnia, and nervousness that appear within a few days of the head trauma. Mild head trauma patients normally make a full recovery, but the process may take months if diffuse axonal injury occurred.

In moderate TBI (GCS scores 9–12), the patient often is stuporous, poorly verbalizes, and opens the eyes to pain. Other signs of trauma (skin lacerations, fractures, etc.) are common. These patients require immediate care, with special attention to possible neck injuries and should be taken to an emergency room for further observation and neuroimaging. Recovering patients frequently com-

plain of headaches, poor recent memory, inability to concentrate, unsteadiness, or vertigo for varying lengths of time.

In severe TBI (GCS scores 3–8) the patient is comatose and unable to open his or her eyes and follow verbal commands. The presence of trauma elsewhere in the body is common. These patients may have severe bleeding, hypotension, and hypoxia that require emergency management. It is common for these patients to worsen over hours as secondary injury events develop. Once comatose, patients may remain unresponsive for hours, days, or weeks. A few patients never regain consciousness and evolve into a persistent vegetative state (permanent coma with return of spontaneous breathing and other brainstem reflexes).

A few patients will have initial loss of consciousness followed by a lucid interval, followed by deterioration of consciousness. The initial loss of consciousness is due to the impact of the head trauma and the second is due to an epidural hematoma. This scenario develops in about 1/2 of

patients with epidural hematoma; the others do not regain full consciousness before deterioration. An epidural hematoma develops most frequently from a linear skull fracture that causes laceration of a branch of the middle meningeal artery (Figure 18-2).

### Major Laboratory Findings

Neuroimaging in the emergency room is usually done to evaluate for neck fractures, skull fractures, and intracranial hematomas. Most often this involves initial cervical spine x-rays followed by a cranial noncontrasted CT. If a depressed skull fracture (bone completely beneath the skull vault and often penetrating into the brain) is detected, surgery is required. Open fractures where there is a connection from the skin surface to the brain increase the risk of intracranial infection (subdural infection [empyema], meningitis, or brain abscess).

The risk of a subdural or epidural hematoma is low (1/1,000) if no fracture is identified but rises to 1/30 if a fracture is seen. Since secondary brain injury may be delayed, repeat CT scans are often required as new signs develop.

The EEG immediately after injury shows suppression of electrical activity over the injured brain that returns as generalized, large-amplitude, slow waves ( $\delta$ ). Depending on the severity of the TBI, the EEG can return to normal.

### Principles of Management and Prognosis

Optimal treatment of the TBI patient has yet to be established. The amount of primary brain injury is determined at the time of trauma. However, the outcome can be improved by minimizing secondary brain injury. One important way is by controlling increased ICP and preventing cerebral

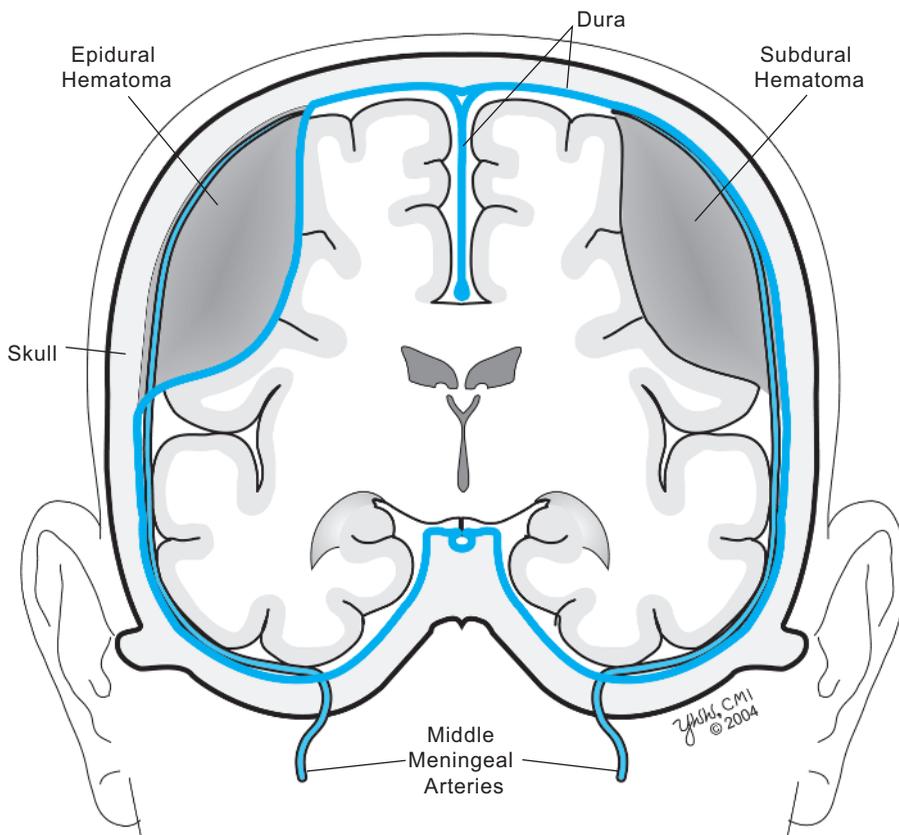


Figure 18-2 Diagram of epidural and subdural hematomas.

ischemia. Diffuse cerebral ischemia occurs when the cerebral perfusion pressure is inadequate. This is particularly important, since TBI often results in loss of cerebral autoregulation of blood pressure, making brain perfusion dependent on cerebral perfusion pressure. Cerebral perfusion pressure is defined as “(mean arterial pressure) – (intracranial pressure).” Thus a fall in systemic blood pressure or a rise in ICP decreases cerebral perfusion pressure. Brain ischemia occurs when the cerebral perfusion pressure is <70 mm Hg, which corresponds to a cerebral blood flow of <40 mL/100 g of brain per minute. Studies have shown that hypotension (systolic blood pressure <90 mm Hg), elevated ICP (above 20–25 mm Hg), and hypoxia (arterial PaO<sub>2</sub> <65 mm Hg, with digital pulse oximetry oxygen saturation of <90%) are the major causes of diffuse brain ischemia. Elevated ICP comes from intracerebral hemorrhages, extracerebral hematomas, and cerebral edema. Normal ICP is 0 to 10 mm Hg; >20 mm Hg is considered sufficiently abnormal to treat.

Prevention of secondary injury begins at the scene of the accident. Studies have shown that up to 1/3 of patients with severe TBI experience hypotension or hypoxia before reaching a hospital; the hypotension doubles the morbidity and mortality. Thus management of the ABCs is essential (see Chapter 16, “Coma and Cerebral Death”). All moderate-to-severe TBI patients should receive nasal oxygen, and the systolic blood pressure should be maintained >90 mm Hg. In the case of cervical spine fractures, intubation should occur without neck extension. If signs of impending herniation are present (dilated and fixed pupil or decerebrate posturing), emergency hyperventilation is started.

In the emergency room following stabilization of the patient, a noncontrast CT is performed. If surgical lesions are identified (subdural or epidural hematoma, large intracerebral hematoma, or depressed skull fracture), the patient usually goes to the operating room. Since measurement of ICP plays a key role in the management of severe TBI, many neurosurgeons place an ICP monitor to follow changes.

The goal is to maintain ICP <20 mm Hg, but most medical management methods reduce ICP only temporarily. Elevation of the head to 30° may help. Mannitol given in intravenous boluses will lower ICP and can be continued until the

serum osmolality reaches 320 mmol/L. At >320 mmol/L, mannitol loses its effect and serum electrolytes become deranged. Hyperventilation will reduce ICP, but its use is controversial since it does so by lowering arterial PCO<sub>2</sub> and constricting cerebral blood vessels. Long-term use of hyperventilation is thought to worsen diffuse cerebral ischemia and hence prognosis. Drainage of CSF through a ventricular pressure monitor catheter will also reduce ICP. If the ICP cannot be controlled by standard medical management or by surgical removal of any hematomas, iatrogenic anesthetic coma with barbiturates can be considered since barbiturate coma can somewhat protect neurons from ischemia. Corticosteroids and hypothermia have not been shown to be beneficial.

The arterial blood pressure should be maintained >90 mm Hg and treated aggressively if hypotension develops. Patients with prolonged coma will require nasogastric feeding to maintain nutrition. Since subdural and epidural hematomas may develop late, repeat CT scans may be necessary if the ICP rises or if the patient deteriorates.

About 5% of TBI patients will experience a generalized seizure during their hospitalization, but prophylactic use of anticonvulsants has limited benefit. Following hospitalization, 5% of patients subsequently develop posttraumatic epilepsy (focal or primarily generalized seizures) that requires anticonvulsants.

The prognosis of TBI depends on its severity. In severe TBI (GCS scores 3–8), there is a linear correlation between admission GCS and poor outcome (death, vegetative state, and neurologic disability). Other poor early prognostic indicators include age >60 years, hypotension on admission, and a fixed dilated pupil. The duration of coma, severity of ICP, and development of hypotension correlate with poor patient outcomes. Of hospitalized patients with severe TBI, 20% die and many survivors have residual neurologic deficits. Rehabilitation of these patients is slow and difficult. Patients may complain of headaches, poor concentration, cognitive deficits, and impulsivity. In adults with severe TBI, unemployment at 5 years is about 70% compared with a 14% preinjury unemployment rate. In children who survive severe TBI, behavioral and learning problems may be a consequence of loss of cognitive skills and poor concentration.

However, under federal special education laws, a child who has a TBI is eligible for free and appropriate public school education and related services.

## Chronic Subdural Hematoma

### Introduction

A subdural hematoma (SDH) may be acute, subacute (signs appear within 1 to 3 weeks of head trauma), or chronic (signs appear more than 3 weeks after trauma). Acute SDHs develop within 1 week following moderate-to-severe TBI or in patients with bleeding diatheses and are discussed earlier in this chapter. This section will discuss those patients who develop chronic SDHs following mild or inapparent head trauma.

The incidence of SDH is rare in small children, lowest in young adults (1/100,000 and usually follows moderate-to-severe TBI), and highest in the elderly (7/100,000). In young adults the male-to-female ratio is 3:1 while in the elderly it is 1:1. Chronic SDH mainly develops from head trauma (motor vehicle accidents; falls from syncope, ataxia, weakness, or seizures; or child abuse), but can occur in patients with bleeding problems (anticoagulation, thrombocytopenia, liver failure, and alcoholism), dural lesions (sarcomas, arteriovenous malformations, and metastatic cancer), and low CSF volume (CSF shunts, renal dialysis, and excess diuretics).

### Pathophysiology

An SDH begins in the subdural space between the dura mater and arachnoid mater of the meninges. The dura intimately adheres to the inner table of the skull and consists of a thick layer of fibroblasts and extracellular collagen. Inner border cells connect directly with the outer layer of the arachnoid membrane. The arachnoid is more vascular and contains blood vessels with tight junctions that arise from meningeal vessels in the internal carotid and vertebral artery system. Blood leakage from tears of arachnoid venules initiates the hematoma.

In infants and small children whose brain is growing, the cerebral cortex abuts tightly against the dura, preventing movement of the brain apart from the skull. As such, a stretching of these blood vessels does not occur, making SDHs rare.

In adults, there is a slowly progressive, age-dependent, atrophy of the brain. From age 50 to 80 years the normal brain shrinks by 200-g weight and the space between the brain and skull increases by 10% of total intracranial space. In addition, many degenerative brain diseases accelerate brain atrophy. Since the skull does not involute, the smaller brain enables independent movement of the two during head trauma that can lead to a shearing or tearing of small arachnoid venules. The existence of anticoagulation promotes a prolonged oozing of blood into the subdural space.

Once present, the subdural blood may expand rather than shrink, as a bruise would do elsewhere in the body. Within days, fibroblasts from adjacent blood vessels begin forming a capsule around the hematoma. New vessels that nourish the capsule and enter the hematoma lack a blood–brain barrier. This neovascularization is “leaky,” allowing RBCs and protein to enter the hematoma. Secondary clotting changes from increased tissue plasminogen activator and diminished plasminogen activator inhibitor also contribute to hematoma expansion in a poorly understood manner. Hence, the hematoma expansion appears to be due to recurrent small hemorrhages into the hematoma (20%) and/or from leaky neovascularization of the hematoma (80%).

Over weeks to months many hematomas continue to expand until they eventually displace sufficient underlying brain tissue to cause signs and symptoms. Untreated, the SDH will continue to shift intracranial structures until coma and brain herniation occur. In others, there is stabilization of the clot with slow clot resolution unless subsequent head trauma causes a new hemorrhage into the subdural hematoma.

The majority of SDHs develop over the lateral aspect of the cerebral convexities but they rarely occur in the posterior fossa.

### Major Clinical Features

In a chronic SDH, signs and symptoms slowly develop over weeks. Headache occurs in >90% of patients and may be lateralizing, constant, and relatively mild. As ICP increases, they often note a deterioration of mental status, with confusion, lethargy, and memory disturbances. This is partic-

ularly common in the elderly. A progressive hemiparesis develops in about 1/2 of patients and aphasia is found in 20%. Focal or generalized seizures occur in 10%. The signs and symptoms of a chronic SDH are not specific; 40% are initially misdiagnosed as other diseases such as Alzheimer's disease, vascular dementia, stroke, depression, or brain neoplasm. In general, SDH should be considered in the elderly who have progressive deterioration of mental status, hemiparesis, and new-onset headache.

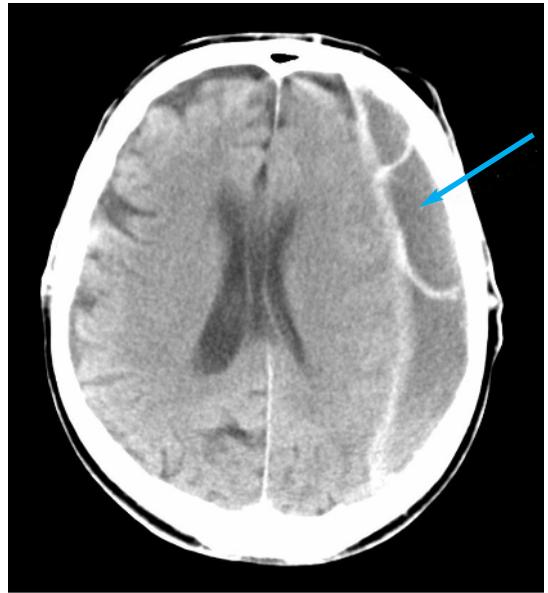
### Major Laboratory Findings

Neuroimaging is the key to the diagnosis. The CT scan demonstrates an oval hematoma between the dura and brain and, depending on the age of the hematoma, has differing densities (Figure 18-3). Acute SDH looks hyperdense relative to brain tissue. Subacute SDH appears isodense (same density as adjacent brain) and is recognized by lateral ventricle compression and shifting, medial displacement of the gray–white junction, and loss of sulcal spaces that normally are seen against the skull table. Chronic SDHs are hypodense (75%) or have mixed densities (25%), suggesting recurrent bleeding into the hematoma. SDHs on T1-weighted MRI images are hyperintense. On T2-weighted images, the hematoma acutely is hypointense, becoming hyperintense after 2 weeks.

The EEG typically shows nondiagnostic suppression of activity and slow waves in the area of the hematoma.

### Principles of Management and Prognosis

Typical management of a symptomatic SDH is drainage of the hematoma by craniotomy; this usually is performed when the hematoma has solid clots or is associated with recurrent bleeding, tumor, or possible infection. Surgical complications include recurrent hematoma, infections, and air under pressure in the meninges or ventricles (tension pneumocephalus) from incorrect placement of the drain. Recurrent hematoma often occurs when marked brain atrophy prevents the brain from reexpanding to the inner table of the skull. In an emergency, twist drill burr holes can be made to relieve ICP. In 1 study



**Figure 18-3** Computed tomography scan of chronic subdural hematoma with mixed densities. (Courtesy of Blaine Hart, MD)

the outcome of surgery for symptomatic SDH was good in 86% of patients, with moderate disability in 10%, severe disability in 2%, and death in 2%. The time to maximum recovery can be within days in younger patients and months in the elderly.

As a consequence of frequent hematoma recurrence in the very old or in patients with disease-induced brain atrophy, a decision must be made whether to operate and remove all the SDH. Indications for observation include no major shift of mid-line structures, no marked new neurologic signs from the baseline, and incidental discovery by neuroimaging.

### RECOMMENDED READING

- Chen JC, Levy ML. Causes, epidemiology, and risk factors of chronic subdural hematoma. *Neurosurg Clin N Am* 2000;11:399–406. (Entire issue devoted to chronic subdural hematoma.)
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# 19 NEUROLOGIC COMPLICATIONS OF ALCOHOLISM

## Overview

Alcoholism, the addiction to alcohol, is characterized by a craving of alcohol and a tolerance to its intoxicating effects. Worldwide, alcoholism has an enormous impact on society, as it is the number one abused drug in the world. In the United States, there are an estimated 8 million people who are alcoholics. About 20% of hospital admissions involve medical complications of excessive drinking. The cause of alcoholism remains poorly understood but genetic factors appear to play a role, as alcoholism is 7 times more frequent in first-degree relatives of alcoholics than in the general population. Adoption studies in Sweden found that alcoholism in a biologic parent was more important than growing up in an environment with alcoholism in the adoptive parents. Identical twins have a higher concordance for alcoholism than fraternal twins.

Ethanol enters the circulation within minutes of consumption and rapidly distributes throughout the body. The liver metabolizes over 95% of alcohol via alcohol dehydrogenase, which converts ethanol into acetaldehyde, which is in turn metabolized by aldehyde dehydrogenase into acetate. In the average adult, alcohol metabolizes at a rate of 8 g/h (~8 oz beer/h). Alcohol consumption at faster

rates leads to increasing alcohol levels in the blood and brain.

The effects of ethanol on the nervous system are numerous and complex. Which brain interactions are responsible for specific ethanol syndromes remains unclear. Ethanol enters cell membranes, increasing membrane fluidity and possibly interfering with signal transduction. Significant components of the withdrawal syndrome after chronic alcohol use reflect reduced neurotransmission in the inhibitory type A GABA pathways and enhanced neurotransmission in glutamate (NMDA) pathways. Alcohol withdrawal causes complex decreases in GABA receptor binding, resulting in loss of presynaptic inhibitory control. During alcohol withdrawal, increased dopaminergic transmission may cause hallucinations and increased autonomic activity. Hypomagnesemia and hypocalcemia frequently occur during alcohol withdrawal and likely contribute to CNS hyperexcitability by altering neuronal action potentials.

Complications of alcoholism involve many organs, but damage to the CNS and PNS is particularly common. This chapter will review the major neurologic complications from alcohol intoxication and withdrawal (Figure 19-1).

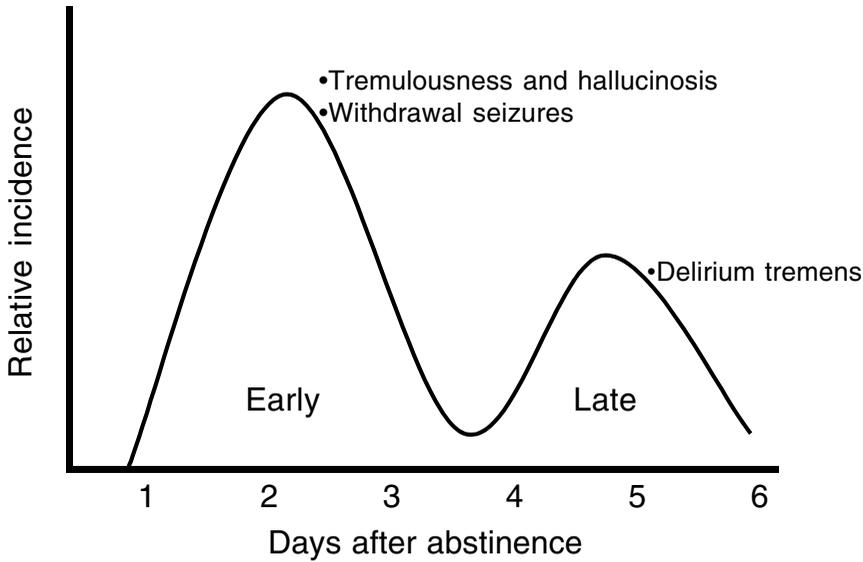


Figure 19-1 Time course of alcohol withdrawal.

## Drunkenness and Alcoholic Coma

Ethanol readily crosses the blood–brain barrier, enabling brain alterations to begin soon after drinking. Signs of intoxication in nonalcoholic persons begin at blood levels of approximately 60 mg/dL; gross intoxication occurs at levels of 120 to 150 mg/dL. In alcoholics, intoxication may not occur until blood levels are as high as 150 mg/dL. Signs of intoxication consist of varying degrees of euphoria, exhilaration, excitement, loss of restraint, irregular behavior, slurred speech, incoordination of movement, gait ataxia, irritability, and combativeness. While the biochemical effects are incompletely understood, the net result appears to be excitation of brain activity. Consumption of large volumes of beer (beer is hypotonic and ethanol inhibits antidiuretic hormone) may produce a sufficient degree of hyponatremia to cause a generalized seizure.

At higher blood levels, brain functions deteriorate, with the development of lethargy, stupor, and coma, suggesting ethanol now produces inhibition of brain activity. Alcoholic coma is seen at blood levels around 300 mg/dL and respiratory failure develops at levels of >400 mg/dL. Comatose patients often require intubation and mechanical ventilation until the alcohol level lowers.

## Alcoholic Tremulousness and Hallucinosis

When alcohol is abruptly reduced, a hyperexcitable withdrawal syndrome develops. The symptoms of alcohol withdrawal can be divided roughly into those from autonomic hyperactivity (tremulousness, sweating, nausea, vomiting, and anxiety) and from neuronal excitation (confusion, agitation, delusions, hallucination, and seizures).

Tremor (“shakes” or “jitters”) develops in over 50% of individuals in withdrawal. The tremors begin about 6 hours after the last drink and worsen over the next 2 to 3 days (Figure 19-1). The tremor occurs at rest and with action, and is coarse, irregular, and increases with stress. Patients may also have an increased startle response. The mental status remains relatively clear, but the patient feels uncomfortable. The tremor abates with consumption of more ethanol or use of benzodiazepines.

Alcoholic hallucinosis occurs in 10% of patients in alcohol withdrawal and typically begins from 24 to 36 hours after drinking cessation. Disordered perceptions of vision or sound develop that may frighten or amuse the patient. Occasionally, frank hallucinations occur. Patients feel “shaky” inside, develop tachycardia, and complain of general weakness and insomnia but do not become agi-

tated. This clinical picture persists for several days to weeks. Use of benzodiazepines again relieves most symptoms.

## *Alcohol-Withdrawal Seizures*

Alcohol-withdrawal seizures occur in nearly 5% of individuals who have been drinking steadily for years and then abruptly stop. For example, undiagnosed alcoholics who are hospitalized may experience a seizure the day after admission. The primarily generalized seizure occurs 7 to 72 hours after alcohol cessation, with a peak at 12 to 48 hours (Figure 19-1). Patients tend to have 1 to 4 seizures over several hours. Status epilepticus is rare.

Alcohol-withdrawal seizures are partly a diagnosis of exclusion. The mechanism for withdrawal seizures is unknown but thought to result from a hyperactive brain (due to alcohol withdrawal), accompanying low serum magnesium, and elevated arterial pH from respiratory alkalosis. In keeping with this,  $1/2$  of patients withdrawing from ethanol have an abnormal EEG manifesting myoclonic or convulsive responses to flashing lights.

Of patients brought to the emergency room with possible alcohol-withdrawal seizures, 50% have another identifiable etiology. These patients often have a seizure aura (implying a focal origin for the seizure), history of serious head trauma while intoxicated, atypical seizures, abnormal neurologic exam, or signs of systemic infection. Neuroimaging studies can identify subdural hematomas, hemispheric contusions or infarctions, intracerebral masses (brain abscess, neurocysticercosis, tumors, and vascular malformations), or meningitis. In patients with known epilepsy, some seizures are actually triggered by drinking alcohol and stopping their anticonvulsant medications. Neurologic exam should not show acute signs that cannot be attributed to chronic alcohol usage. The blood alcohol level should be 0 or very low and the CSF exam, if done, is normal.

Administration of benzodiazepines (lorazepam or diazepam) to patients during alcohol withdrawal usually prevents further seizures during the critical withdrawal period. Phenytoin administration does not prevent seizures. Patients who permanently stop drinking do not have future seizures. Controversy exists as to whether administration of anticonvulsants prevents subsequent

alcohol-withdrawal seizures. Since patients often stop their anticonvulsants during drinking spells, the combination of alcohol and anticonvulsant withdrawal may actually increase their risk of future seizures.

## *Delirium Tremens*

Delirium tremens (DTs) is a serious but uncommon complication of alcohol withdrawal (less than 5% of hospital admissions for alcoholism) and presents with profound delirium and autonomic nervous system overactivity. Patients have marked confusion, agitation, hallucinations, tremors, and sleeplessness. Signs of increased autonomic nervous system activity include fever, tachycardia, dilated pupils, and profuse sweating. Clinical signs begin 2 to 5 days after alcohol withdrawal and may be preceded by withdrawal seizures (Figure 19-1). Life-threatening events include high fever, dehydration, hypotension, cardiac arrhythmias, and secondary complications of trauma (from the agitation) or alcohol-associated medical conditions (liver failure, GI bleeding, systemic infection, or pancreatitis).

Treatment aims at reducing agitation and maintaining fluid and electrolyte balance. Lorazepam given repeatedly intravenously or intramuscularly is required for sedation. Patients require fluid replacement of up to 4 to 10 L/24 h to prevent dehydration and circulatory collapse. Serum potassium and magnesium levels are usually low and require correction.

The duration of DTs lasts 2 to 7 days, with most cases ending by day 3. Recovering patients regain alertness and the ability to cooperate but seldom have any memory of the acute illness. The mortality rate is 10%.

## *Wernicke's Encephalopathy and Korsakoff's Psychosis Syndrome*

### **Introduction**

Wernicke's encephalopathy and Korsakoff's psychosis are linked to abnormally low levels of thiamine (vitamin B<sub>1</sub>) in the CNS. Chronic alcoholic patients tend toward malnourishment. People with alcoholism may obtain as much as  $1/2$  their daily

caloric intake from ethanol, resulting in serious nutritional deficiencies, including thiamine, niacin, folate, and protein. Hence, these two disorders are not linked to the direct toxic effects of alcohol or alcohol withdrawal. Thiamine is required for all tissues and is found in high concentration in the brain, heart, skeletal muscle, liver, and kidney. Thiamine is absorbed in the small intestine and transported to the brain by an energy-dependent transport system. A series of phosphorylation reactions produces thiamine diphosphate, a required cofactor in carbohydrate and amino acid metabolism. Thiamine-dependent enzymes are involved in the biosynthesis of neurotransmitters and for the production of reducing equivalents used in oxidant stress defenses.

Manifestations of thiamine deficiency can involve the brain (Wernicke–Korsakoff syndrome), peripheral nerves (dry beriberi), or the cardiovascular system (wet beriberi).

### Pathophysiology

Neuropathologic findings in Wernicke’s encephalopathy include demyelination, glial and vascular proliferation, hemorrhage, and necrosis. These principally affect gray-matter regions of the medial thalamus, hypothalamus, tegmentum of the pons and medulla, and cerebellum (particularly the Purkinje and granule cells of the anterior-superior vermis). Korsakoff’s psychosis shows pathologic brain changes, including hemorrhages and necrosis in the dorsomedial nucleus of the thalamus and/or the mamillary bodies.

### Major Clinical Features

Wernicke’s encephalopathy is a disease of acute or subacute onset and is characterized by nystagmus, abducens and conjugate gaze palsies, gait ataxia, and a confusional state. The ocular signs consist of nystagmus that is both horizontal and vertical, paralysis of external recti, and paralysis of conjugate gaze. Nystagmus and weakness of the lateral rectus muscles are the most common; total ophthalmoplegia is rare. The ataxia of stance and gait typically produces a wide-based, unsteady, short-stepped, lurching gait. Ataxia of limbs remains less pronounced, and many patients have normal finger-to-nose and heel to shin tests.

Most patients experience a quiet confusional state characterized by apathy, inattentiveness, and

indifference to surroundings. Speech is minimal. Drowsiness is common and may progress to stupor if untreated. Mild disorders of perception or hallucinations are experienced by 20% of patients.

Korsakoff’s psychosis is a unique mental state in which retentive memory is impaired out of proportion to other cognitive functions in an otherwise alert, fluent, and responsive patient. A selective disorder of memory, Korsakoff’s psychosis typically follows  $\geq 1$  episodes of Wernicke’s encephalopathy. Impaired memory for previously established recent events (retrograde amnesia) and the inability to incorporate new memories (anterograde amnesia) appears, but immediate recall stays preserved. Patients, while disoriented to place and time and unaware of their memory deficits, confabulate or invent material to fill in memory gaps.

### Major Laboratory Findings

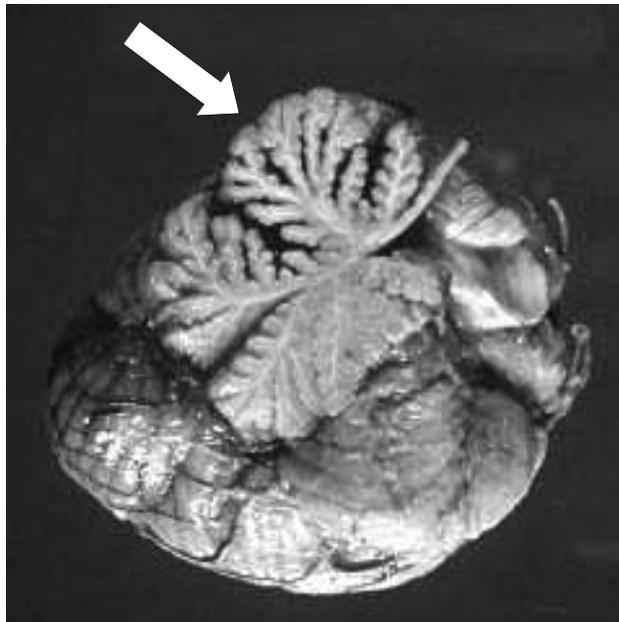
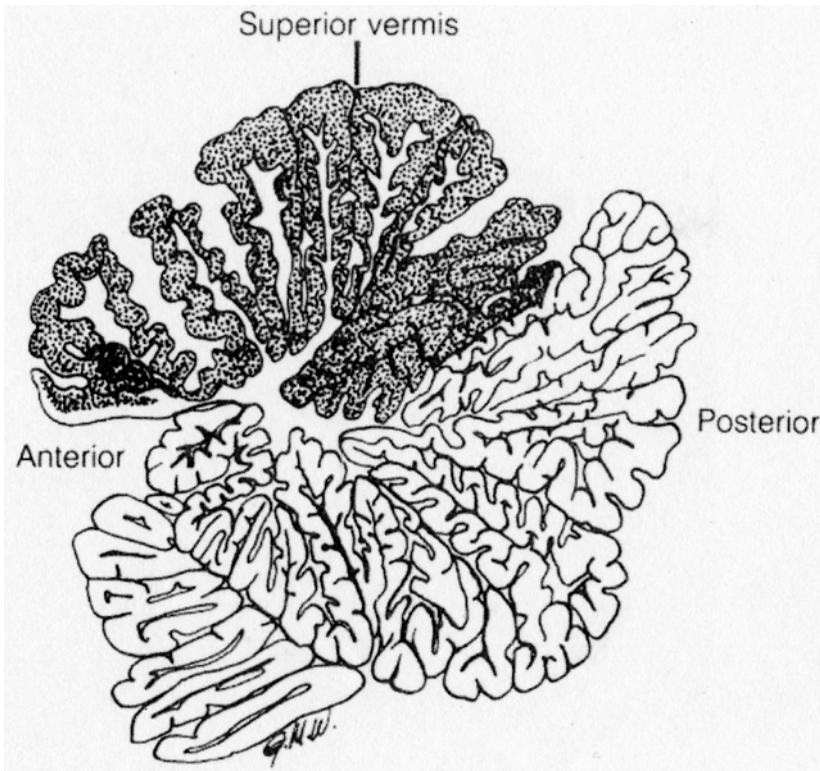
MRI abnormalities vary in acute patients and include T2-weighted abnormalities in the periaqueductal region, medial thalamus, and mamillary bodies. Later, the T2-weighted abnormalities disappear and atrophic changes occur in the mamillary bodies and cerebellar vermis, with enlargement of the third ventricle.

### Principles of Management and Prognosis

Early diagnosis of Wernicke’s encephalopathy is critical, as administration of intravenous thiamine can correct the acute neurologic problem. In fact, it is prudent to administer parenteral thiamine to every alcoholic patient seen in the emergency room or hospitalized, since administration of glucose can precipitate the onset of Wernicke’s encephalopathy. It is less clear whether thiamine can reverse the memory deficit seen in Korsakoff’s psychosis. Poor prognostic factors include severe clinical features, delayed thiamine administration, T2-weighted abnormalities on MRI, and cerebellar or mamillary body atrophy. In countries using thiamine-enriched flour in bread, the incidence of Wernicke–Korsakoff syndrome has fallen but not disappeared.

### Alcoholic Cerebellar Degeneration

Chronic alcoholism often leads to slowly progressive gait ataxia similar to that seen in Wernicke’s encephalopathy. This is a wide-based, unsteady,



**Figure 19-2** Alcoholic cerebellar degeneration.

short-stepped, and lurching gait. Patients often run their hands against the side of buildings or walls to improve their ambulation. Limb ataxia is usually mild. MRI shows atrophy of the superior

cerebellar vermis and pathology demonstrates a loss of cerebellar Purkinje cells and other neurons, maximally in the superior vermis and vestibular nuclei (Figure 19-2). Once gait ataxia

develops, no treatment has been shown to reverse it.

## Alcoholic Polyneuropathy

A distal symmetrical sensorimotor polyneuropathy is common in chronic alcoholism. The etiology of the neuropathy remains unclear, although direct effects of alcohol on the peripheral nerve and nutritional/vitamin deficiencies have been proposed.

The majority of patients have slowly progressive symptoms of paresthesias, burning dysesthesias, numbness, and muscle cramps in their feet and lower legs. On exam, there is a loss of ankle jerks, diminished vibratory sensation in the feet, and varying degrees of foot numbness and weakness. Loss of pain sensation appears less commonly. As the disease advances, leg weakness and gait apraxia occur from loss of position sense in the feet and possibly concomitant alcoholic cerebellar degeneration. Axonal degeneration, the principal pathologic process, occurs although segmental demyelination can occur. If alcohol consumption stops, the neuropathy may improve. Use of simple analgesics and tricyclic antidepressant medications may alleviate the burning dysesthesias.

## Fetal Alcohol Syndrome (FAS)

### Introduction

Alcohol is the most common human teratogen. Of the 60% of women who drink alcohol, 16% report drinking during their pregnancy and 4% report drinking more than 7 times per week. An estimated 0.5% (500/100,000) of all live births have some prenatal alcohol damage.

### Pathophysiology

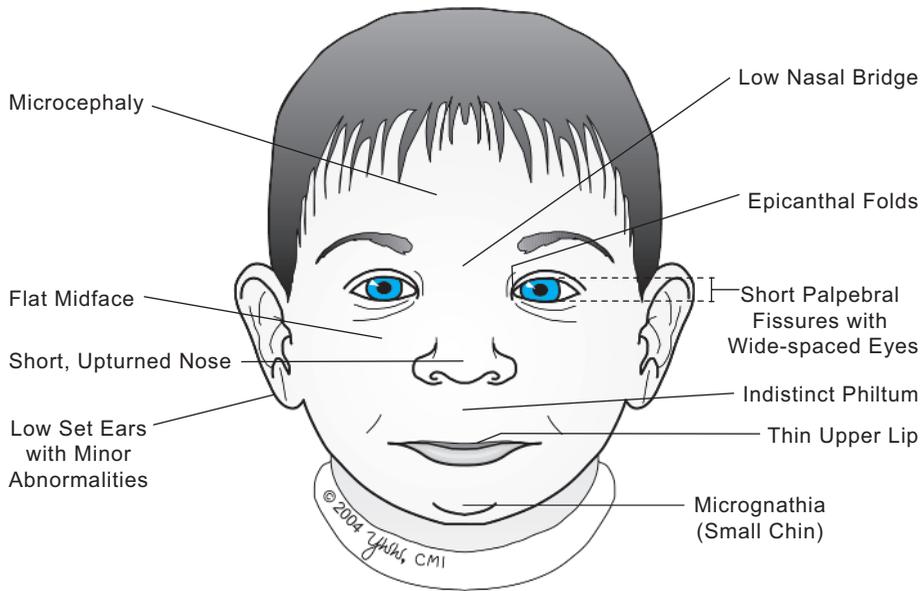
The pathophysiology of FAS, while incompletely understood, has several generalizations. Human and animal studies have found that (1) consumption of  $\geq 1$  alcoholic drinks per day is highly associated with FAS, (2) alcohol exposure in the first trimester of pregnancy leads to the characteristic congenital malformations of the face and midline brain, (3) third-trimester alcohol exposure decreases

brain weight and numbers of neurons, and (4) peak blood alcohol concentrations are more critical than the same dose of alcohol at a lower peak level. The threshold amount of alcohol consumption needed to produce fetal toxicity remains unknown. As such, total abstinence from drinking alcohol is currently recommended for pregnant women and women planning pregnancy.

How alcohol damages the developing fetal brain is poorly understood, but it can kill developing neurons. In early development, excessive cell

**Table 19-1 Characteristic Features of Fetal Alcohol Syndrome**

<b>Facial Abnormalities</b>
Short palpebral fissures Ptosis (droopy eyelids) Flat mid-face Smooth philtrum Thin upper lip
<b>Growth Retardation</b>
Low relative birthweight Growth retardation despite adequate nutrition Low weight relative to height
<b>Central Nervous System Neurodevelopmental Abnormalities</b>
Microcephaly Agenesis of corpus callosum Cerebellar hypoplasia Neurologic signs that may include poor fine-motor coordination, hearing loss, and clumsy gait
<b>Behavioral Abnormalities</b>
Learning disabilities (poor abstract reasoning, math skills, judgment, concentration, and memory) Poor school performance Poor impulse control Hyperactivity Poor social interactions
<b>Birth Defects</b>
Congenital heart defects Skeletal and limb abnormalities Ophthalmologic abnormalities Sensorineural hearing loss Cleft lip or palate



**Figure 19-3** Fetal alcohol syndrome.

death in the mid-line of the developing embryo may account for mid-line brain defects (agenesis of corpus callosum) and craniofacial abnormalities. In late fetal development, the loss of neurons is more widespread, producing a low brain weight. Hypotheses of the mechanism by which ethanol kills neurons includes formation of toxic acetaldehyde by alcohol dehydrogenase metabolism of ethanol; free-radical formation, which causes cellular damage in the developing brain; and disruption of the L1 cell adhesion molecule (CAM), which is important in the developing brain.

### Major Clinical Features

Infants with FAS demonstrate several characteristic abnormalities that involve growth retardation, craniofacial structure, neurodevelopmental abnormalities, behavioral problems, and occasional birth defects (Table 19-1 and Figure 19-3). The average IQ score in FAS is 66, with a range of 16 to 105. These IQ scores are higher than those seen in Down syndrome (25–65) and fragile-X syndrome (30–55). Nearly 60% of FAS children develop significant behavioral problems compared with 25% for Down syndrome children. The cognitive, behavioral, and psychosocial problems persist into adulthood.

### Major Laboratory Findings

Clinicians have created categories such as alcohol-related birth defects and fetal alcohol effects or alcohol-related neurodevelopmental disorder for infants damaged by ethanol who do not meet all the criteria for FAS. Presently there is no laboratory test that establishes the diagnosis.

### Principles of Management and Prognosis

Patient management begins with an early diagnosis that enables medical intervention, psychologic help, educational evaluation, and access to special education and related services such as speech and language programs and community resource programs. Helping the mother and other family members enables family preservation and helps prevent drinking during subsequent pregnancies.

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## 20 DISORDERS OF PAIN AND HEADACHE

### *Pain*

Pain and headache are symptoms and not diseases. Like weakness and dizziness, pain has many causes that must be sorted out by careful history and exam.

### **Overview**

Pain, a highly complex perception, is more than a sensory experience warning of danger. The perception of pain is influenced by environment and by emotion as well as by complex and incompletely understood pathways that have multiple regulatory controls. The following simplification of the immensely complicated pain system is useful in understanding the types of pain patients may experience.

Pain pathways appeared at different times in evolution for potentially different purposes. The most primitive system uses polymodal nociceptors activated by a variety of high-intensity mechanical, chemical, and thermal stimuli. These nerve fibers are small-diameter, unmyelinated C fibers that conduct slowly at 0.5 to 2.0 m/s. They fire continuously without decay if the noxious stimulus is maintained. Activation of C fibers is appreciated as a burning, uncomfortable, poorly localized

pain. C fibers travel to the dorsal root ganglion and terminate in the outer layers of the dorsal horn of several adjacent segments of the spinal cord. They release glutamate and substance P as their excitatory neurotransmitters. In the periphery, pain fibers also may release a variety of peptides, including substance P, bradykinin, serotonin, and prostaglandin, which induce local inflammation. These, in turn, trigger firing of adjacent pain nociceptors, thus amplifying the intensity of the pain signal and expanding the skin area involved.

In the dorsal horn, interneurons modulate propagation of the upward pain signals. The signal may be diminished or inhibited by interactions from endorphin interneurons (endogenous opioids) or by concomitant signals coming from peripheral A $\delta$  pain fibers. The pain signal may also be amplified by a less-understood mechanism called central sensitization. Many pain drugs, such as opioids, tricyclic antidepressants, and capsaicin, act, in part, at the dorsal horn.

There are 2 major pathways for the central transmission of pain signals. The first uses the spinomesencephalic pathway, where pain fibers project from the dorsal horn to the mesencephalic reticular formation and periaqueductal gray region of the mid-brain. Signals may also travel via the second spinoreticular (contralateral and ipsi-

lateral) pathway from the dorsal horn to reach the reticular formation of the medulla and pons. Some of these impulses eventually reach the thalamus and somatosensory cortex. Both pain pathways interact with interneurons, where again pain modulation occurs. The periaqueductal gray region is rich in endorphin-containing interneurons that can inhibit pain signals. This brain area is also a target for pain medications. Morphine activates opioid receptors and affects descending pathways that control nociceptive inputs. Both central pathways are thought to be responsible for slower, more diffuse, burning types of pain sensation. It is dysfunction of this complex pain pathway that commonly produces the chronic disagreeable pain so disruptive to the lives of many patients.

The most recent evolutionarily pain pathway conducts nociceptive pain signals generated by mechanical, thermal, or chemical noxious stimuli all the way to the cerebral cortex and thus into consciousness. This pathway system, more rapid than the primitive pathway, gives more precise localization of the pain source. Stimulation generates signals that are felt as sharp, pricking, localizable pain. Peripheral pain fibers are small-diameter, thinly myelinated A $\delta$  fibers that conduct at 5–30 m/s. These axons usually have dynamic firing rates that decline with time even if the stimulus is maintained (accommodation). These fibers travel to the dorsal root ganglion, terminate in the outer layers of the dorsal horn of the adjacent segments of spinal cord, and release glutamate as the excitatory neurotransmitter. Again, complex interneurons modulate further transmission of the pain signal. Second-order axons in the spinothalamic pain pathway cross the spinal cord mid-line and travel up the contralateral spinothalamic tract to terminate at the thalamus (ventral posterior lateral and central lateral nuclei). Third-order axons then travel to the somatosensory cortex and somatosensory association cortex. What happens after pain signals reach conscious perception is poorly understood. Pathology in this system may give rise to lancinating pains (brief, sharp, intense pains) as seen in trigeminal neuralgia and shingles neuritis.

Spontaneous firing of a sensory nerve may occur from degeneration of a distal sensory nerve, also called dying back neuropathy. This ectopic firing can also occur from nerves adjacent to tissue damage occurring at the nerve ending or proximal

to it. Proximal nerve damage may be from demyelination or local pressure damage, while distal damage may be secondary to infection, etc. If only A $\delta$  fibers fire ectopically, the result is painless paresthesias, like hitting the ulnar nerve at the elbow. If C fibers or both fiber types ectopically fire, the individual may experience dysesthesias, which are spontaneous uncomfortable sensations, or allodynia, which is discomfort from gently rubbing the skin. Hyperalgesia develops when the nociceptor input is amplified peripherally or centrally, yielding more pain than would otherwise be expected.

## Headache Pain

### Overview

For most types of head pain, the first and second divisions of the trigeminal nerve bring noxious signals to the brain and to awareness. Only certain parts of the CNS are innervated by pain fibers. These include all blood vessels (arteries, veins, and sinuses), meninges, bone, and several cranial nerves (CNs V, VII, IX, and X). In addition, the scalp, skull muscles, sinus mucosa, and teeth convey pain signals. However, the brain parenchyma is insensitive to pain. Somatic pain usually localizes to the exact area of injury (e.g., scalp laceration), while the pain from headache is more diffuse and localizes only to large regions of the head.

There are over 250 causes of headache. In general, a simple classification divides headaches into primary and secondary. Primary headaches (like tension type, migraine, and cluster) are those headaches in which pain is the primary symptom and no structural damage occurs to the brain. Secondary headaches (from tumor, infection, subdural hematoma, etc.) develop from structural damage to the skull or CNS masses that generate increased ICP. Secondary headaches may be due to serious conditions and often produce other neurologic signs and symptoms.

The evaluation of a patient with headache usually requires a careful history with attention to its characteristics (Table 20-1). The exam should be thorough, with attention for the presence of papilledema, neck stiffness, cranial nerve signs (especially the trigeminal nerve), signs of sinus or tooth or mouth infection, etc. For the headache to

**Table 20-1** *Important Considerations in Headache Evaluation*

• Headache warning (aura)
• Antecedent event (head trauma or dental/facial infection)
• Headache location
• Headache intensity (mild, moderate, or severe or a Likert scale score of 0 to 10)
• Headache frequency
• Pain character (constant pressure or throbbing; sharp or dull)
• Headache duration (minutes, hours, days, or constant)
• Headache triggers (coughing, sneezing, eating cold food, alcohol consumption, etc.)
• Age of onset of headaches
• Presence of family history of similar headaches
• Presence of other neurologic symptoms, including nausea, vomiting, weakness, loss of facial sensation, hearing changes, vertigo, etc.

be considered primary, the neurologic exam should be normal. If the neurologic exam is abnormal, the headache may be secondary and the result of structural damage of the face, skull, meninges, or brain. If structural damage is suspected, neuroimaging should be considered, especially if the neurologic abnormalities are of recent origin.

## Tension-Type Headache

### Introduction

Tension-type headaches (TTHs) are the most-common type of headache, with a lifetime prevalence of 78% and a yearly prevalence of 38%. About 1/3 of patients with TTH experience 14 or more headaches a year. While the majority of individuals do not seek medical attention and treat the headache with over-the-counter analgesics, about 3% experience severe incapacitating pain or headaches that occur multiple times a week (chronic daily headache). There is seldom a genetic predisposition. The peak prevalence rates occur in young adults. Simple TTHs occur about equally in men and women, but women have twice the rate of chronic daily headaches.

### Pathophysiology

Remarkably little is understood about TTH. We currently do not know the etiology of the headache, the exact structure(s) that generate the pain (myofacial tissues or central brain mechanisms), or whether TTH is part of the migraine spectrum. Currently, there is general agreement that scalp and neck muscles (frontalis, temporalis, pterygoids, masseter, and trapezius) have increased tenderness and possibly thicken during a TTH. However, resting EMG studies of these muscles have not shown increased muscle firing rates compared with nonheadache controls; nonheadache individuals may have tender muscle areas to palpation similar to individuals with TTH. Stress and poor sleep habits may trigger headaches, but the mechanism remains unknown. Elderly individuals with cervical arthritis may experience TTH.

### Major Clinical Features

The typical patient with TTH complains of constant, nonpulsating (75%), bilateral pain (90%), which is localized over the frontal, temporal, and posterior neck muscles (Table 20-2). Usually the headache is not aggravated by physical activity, light, or sound. Nausea and vomiting are uncommon. The headache begins as a dull pain, often in the neck, that slowly progresses in intensity and cranial area over several hours. If the headache becomes intense, it may become unilateral and throbbing in nature. The headache may last from a few hours to all day. Scalp and neck muscles may be tender. Specific headache triggers are seldom identified except for stress, lack or excess of sleep, and missed meals. The neurologic exam during and between headaches should be normal.

### Major Laboratory Findings

Patients with TTH have normal neuroimaging exams, routine blood tests, and normal EEGs.

### Principles of Management and Prognosis

Management of TTH patients is divided into acute treatment and prophylaxis. Most patients treat mild-to-moderate TTH with simple over-the-counter analgesics, such as aspirin, acetaminophen, and nonsteroidal analgesics. Studies generally have

**Table 20-2 Clinical Differences Between Tension-Type and Migraine Headache\***

Symptom	Tension Type	Migraine
Onset	Slow over hours	More rapid
Visual Aura	No	20%
Pain Character	Constant pressure	Throbbing
Location	Bilateral, often in neck and frontalis and temporalis muscles	Unilateral
Nausea and Vomiting	Uncommon	Common
Photophobia	Uncommon	Common
Duration	Hours to years	Hours to 2 to 3 days
Neurologic Signs	No	Only if complicated migraine
Relief from Sleep	Seldom	Frequent

\* Not all headaches demonstrate all properties. Some migraines are bilateral and nonthrobbing and some tension-type headaches will develop migraine-like symptoms if the headache becomes intense or prolonged. It is also common for migraine patients to develop tension-type headaches.

found that all 3 types are about equally effective, especially if taken early in the headache. Muscle relaxants (such as benzodiazepines) and migraine-specific drugs are seldom effective. Narcotics may give temporary pain relief but often do not terminate the headache.

Nonpharmacologic treatments are often effective and include hot and cold packs to the head or neck and hot baths or showers. Acupuncture and spinal manipulation therapy has not been shown to be effective.

If the headache becomes severe, treatment is often difficult as simple analgesics are seldom effective. Stronger analgesics and medications aimed at inducing sleep are often needed.

If headaches become frequent (>15 d/mo), prophylactic treatment is indicated. This may include regular aerobic physical exercise (walking, jogging, or swimming for 20 to 30 min 5 times per week), neck-stretching exercises, and pharmacologic prophylaxis. Tricyclic antidepressants (amitriptyline and nortriptyline) in low doses taken daily are widely used and often successful in reducing frequency and intensity of the headache. Once the headache frequency reduces (usually over weeks to several months), the drugs are then slowly discontinued. A few patients take analgesics in high doses many times daily to control the pain. These individuals are prone to developing a rebound headache when they do not take the analgesic.

Therefore, reduction of chronic analgesic use is warranted. Avoiding caffeine may decrease headache frequency, although caffeine-withdrawal headaches can occur.

It is important for patients to understand the nature of their TTH headache. They should expect recurring headaches that continue for years and the need to develop their own patterns of coping with them.

## Migraine Headache

### Introduction

Migraine headache is a common and often-debilitating disorder that is treatable. The syndrome is characterized by recurrent attacks of headache that vary widely in intensity, duration, and frequency. It is associated with varying amounts of nausea, vomiting, and photophobia. About 28 million Americans suffer from migraine, with a prevalence rate of 18% for adult women and 6% for adult men. Migraine usually begins during adolescence or young adulthood. After the age of 50 years, migraines begin to subside spontaneously. Occasionally children from ages 5 to 10 years also may experience migraines. There is a dominant genetic predisposition to migraines, but specific genes have not been identified.

## Pathophysiology

The etiology of migraine is unknown and the pathophysiology is incompletely understood. Early theories focused on intracranial blood vessels that were thought to vasoconstrict during the migraine aura and dilate during the headache. There is now considerable evidence that active vasoconstriction does not cause the aura.

More-recent theories have focused on the roles of the trigeminal nerve, meningeal blood vessels, and brain in producing a migraine. These hypotheses are labeled the “trigeminovascular theory.” Nerves going to meningeal blood vessels are unmyelinated and contain vasoactive peptides such as substance P, neurokinin A, nitric oxide, and calcitonin gene-related peptide. These are released when the trigeminal nerve is stimulated. In addition, serotonin (5-hydroxytryptamine or 5-HT) receptors are present in meningeal blood vessels and in the trigeminal nerve endings. The trigger for trigeminal nerve stimulation is unknown, but release of these vasoactive peptides triggers a sterile inflammatory response that secondarily stimulates the trigeminal nerve pain fibers. Central brain connections of the trigeminal nerve travel to the brainstem and are thought to activate autonomic responses such as nausea and vomiting. Trigeminal nerve axons traveling to the reticular activating system and cortex are thought to activate the pain responses.

The aura of a migraine is felt to represent a direct cortical event. Abnormal depolarization occurs mainly in the occipital cortex, with neurotransmitter release to adjacent neurons producing a wave of depolarization spreading at 2 to 3 mm/min and producing the typical visual aura. In addition, persistent hyperpolarization of the involved brain area results in reduction of local blood flow to the hyperpolarized brain cells. The term *spreading depression* refers to this phenomenon. The trigger for the aura is unknown.

## Major Clinical Features

Migraine attacks usually occur 1 to 2 times per month. In most there is no recognized trigger. However, triggers noted by patients include consumption of alcohol, excessive salt intake, menstrual periods, use of birth control pills or conjugated estrogen tablets, sleep irregularities, certain foods, and stress or even the resolution of stress.

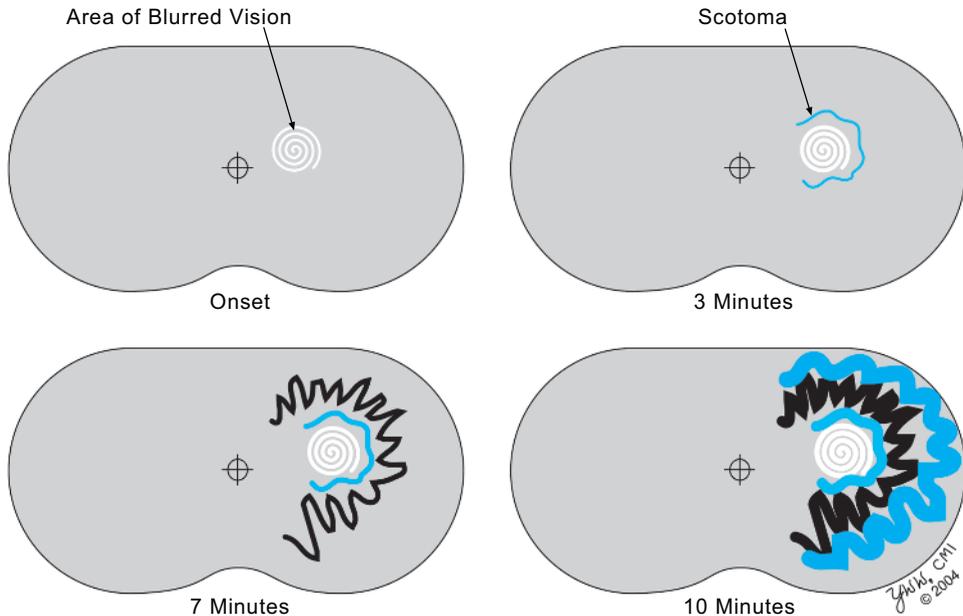
Migraine headaches are divided into 4 phases: prodrome, aura, headache, and postheadache. Occasionally patients have a prodrome and are aware a migraine attack is coming hours before the headache begins. These vague symptoms are often described as irritability, mood changes, fluid retention, polyuria, photophobia, or unusual drowsiness.

About 20% of patients experience an aura that begins 5 to 20 minutes before the headache phase. The aura of most patients is visual, but a few patients have sensory, motor, or aphasic auras. The visual aura usually begins as a vague diminishing or blurriness (not total loss) of vision (like looking through water), with varying amounts of flickering dots of bright white or colored lights that often expand and move into the periphery of one visual field and then disappear (Figure 20-1). A key identifier of an aura is that the lights do not disappear when the eyes are closed. In contrast, most ocular causes of visual disturbance disappear with closure of the eyes.

The headache is usually unilateral (in the frontal or temporal area), pounding, and severe (Table 20-2). The time from headache onset to severe headache is usually less than 1 hour. About 1/4 of patients will describe their severe headache as bilateral or nonthrobbing. Nausea and vomiting are common and may occur early in the headache phase. Patients commonly note photophobia (increased pain from bright light) or phonophobia (increased pain from loud noises). During the headache phase, many find concentration and higher cortical functioning difficult, even if the pain is controlled with medication. Patients often avoid further stimulation of the CNS and frequently seek a dark, quiet room to rest, as sleep often relieves the headache. The headache typically lasts 4 to 24 hours, with occasional headaches lasting up to 3 days. As the headache subsides, some patients experience lingering symptoms of fatigue, difficulty in concentrating, and residual nausea for up to 1 day.

## Major Laboratory Findings

The diagnosis of migraine in an adult patient is usually based on a typical history and a normal neurologic exam. There is no diagnostic test for the disease. Routine blood and CSF exams are normal. PET and fMRI scans may demonstrate focal areas of



**Figure 20-1** Classical migraine visual aura as it progresses over 10 minutes.

mildly reduced blood flow that are not diagnostic. The migraine of patients who experience auras is classified as *migraine with aura* or *classical migraine*. Patients without auras are classified as *migraine without aura* or *common migraine*. Patients who develop prolonged auras or headaches with neurologic signs that persist are classified as *migraine with prolonged aura* or *complicated migraine*. Occasional patients will experience a visual aura without the headache (*migraine equivalent*).

### Principles of Management and Prognosis

Management of patients with migraine headaches is divided into treatment of the acute headache and prevention of frequent headaches.

In many patients, migraine responds well to simple treatment at the time of an attack. Drugs such as aspirin, acetaminophen, ibuprofen, or naproxen should be taken as soon as the headache component of the attack is recognized. A variety of other drugs are aimed at inducing sleep, a potent terminator of migraine. Ergotamine and dihydroergotamine (DHE), 2 ergot alkaloids, are serotonin antagonists and have a high affinity for the 5-HT<sub>1A</sub> and 5-HT<sub>1D</sub> trigeminal nerve receptors. These drugs constrict cerebral and systemic blood vessels and also prevent release of inflammatory

peptide mediators from the trigeminal nerve. Side effects, mainly nausea and vomiting, are common. These drugs work best if given early in the headache phase or during the aura. In some patients, vomiting, nausea, and gastroparesis may prevent systemic absorption of oral medications, making oral treatment ineffective.

In 1990, treatment of headache pain dramatically improved with the introduction of triptan medications that could be delivered by the subcutaneous, nasal, sublingual, and oral routes. Triptans are receptor agonists that act at the 5-HT<sub>1B</sub> receptor located on meningeal blood vessels and appear to inhibit the aseptic perivascular inflammation induced by stimulation of the trigeminal nerve. Triptans may also inhibit transmission through second-order neurons of the trigeminocervical complex. Triptan medication can be given at any time during the headache. Subcutaneous formulations deliver pain relief within 1 to 2 hours in about 3/4 of patients while oral tablets deliver pain relief in 2 to 4 hours in slightly fewer patients. Triptans may cause mild constriction of coronary arteries and thus are contraindicated in patients with ischemic heart disease, Prinzmetal's angina, or the presence of a complicated migraine.

Attempts to reduce the frequency of migraines are usually directed toward patients with  $\geq 4$

headaches per month. Nonpharmacologic therapy is beneficial and aims at encouraging regular aerobic exercise, keeping regular sleeping hours, and avoiding alcohol, caffeine, and other known triggers. The U.S. Headache Consortium identified 4 medications shown to significantly reduce the frequency of migraines on multiple double-blind placebo-controlled trials: amitriptyline, divalproex sodium, propranolol, and timolol. These drugs must be taken daily, have a variety of mild-to-moderate side effects, and often reduce migraine frequency by about 50%. Many other medications have been shown to have some benefit in preventing migraines, but the evidence is less certain and/or side effects are more common or serious.

## RECOMMENDED READING

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## 21 DISORDERS OF THE VESTIBULAR SYSTEM

### Overview

Dizziness and vertigo are especially common in the elderly, but symptoms occur at any age. Dizziness, a nonspecific term, implies a sense of disturbed relationship to the space outside oneself. Patients frequently use such words as imbalance, off-balance, swaying, floating, light-headed, impending faint, giddiness, fuzzyheaded, reeling, and anxiety. Vertigo is an illusion of rotation or body movement through space and implies dysfunction of the vestibular system. Table 21-1 lists the major causes of dizziness and vertigo. In the elderly, multiple causes are often present (multifactorial).

Normal balance comes from appropriate brainstem and cerebellar integration of 3 sensory systems: vestibular, visual, and proprioceptive (Table 21-2). Incorrect sensory signals or inappropriate integration of sensory signals gives rise to dizziness and vertigo.

The vestibular system comprises end organs adjacent to each cochlea (3 semicircular canals [SCCs], utricle, and saccule), vestibular nerves, and vestibular nuclei located in the dorsal medulla at the floor of the fourth ventricle and mid-line cerebellum (Figure 21-1). The vestibular system divides into 2 major components. First, the vestibulospinal system alters body position in

response to changes in gravity. Changes in gravity are detected by the bending of hair cells in the macula of the utricle and saccule when there is movement of otoconia (tiny calcium carbonate crystals embedded in a gelatinous matrix). Impulses sent via the vestibular nerve to vestibular nuclei are processed and then transmitted to anterior horn cells of antigravity muscles to maintain stable body posture. Changes in posture usually occur without an individual's awareness.

Second, the vestibuloocular system maintains steady eye position in space during head movement. Angular acceleration is detected by one or more pairs of the semicircular canals, which are located at right angles to each other. Head rotation bends SCC hair cells in the endolymph, sending a change in baseline frequency of nerve signals to brainstem vestibular nuclei. The signals are integrated, resulting in appropriate signals transmitted via CN III, IV, and VI to move the eyes equally in the opposite direction of head rotation. Thus during head movement, the world does not appear to move. Individuals with vestibuloocular reflex (VOR) dysfunction complain of vertigo when they move their head.

The visual system locates the horizon and detects head movement from the horizon. It also sends feedback (retinal slip) information to the

**Table 21-1 Major Causes of Dizziness and Vertigo**

<p>Vestibular System (25%)*</p> <p><b>Benign paroxysmal positional vertigo</b></p> <ul style="list-style-type: none"> <li>Meniere’s disease</li> <li>Vestibular neuritis</li> <li>Chronic labyrinthine imbalance</li> </ul>
<p>Proprioceptive System (15%)</p> <p><b>Distal sensory peripheral neuropathy</b> (diabetes, alcohol, and toxic compounds)</p> <ul style="list-style-type: none"> <li>Pernicious anemia (Vitamin B<sub>12</sub> deficiency)</li> <li>Spinocerebellar ataxia</li> <li>Human immunodeficiency virus myelopathy</li> </ul>
<p>Visual System (&lt;1%)</p> <ul style="list-style-type: none"> <li>Recent unrecognized diplopia or cataracts</li> </ul>
<p>Brainstem or Cerebellum (25%)</p> <p>Structural (1%)</p> <ul style="list-style-type: none"> <li><b>Infarction</b> (lateral medulla or mid-line cerebellum)</li> <li>Tumor (glioma, ependymoma, etc)</li> <li>Degenerative (multisystem atrophy)</li> <li>Congenital (Arnold–Chiari malformation)</li> </ul> <p>Metabolic (24%)</p> <ul style="list-style-type: none"> <li><b>Cardiovascular</b> (orthostatic hypotension, vasovagal syncope, cardiac arrhythmia, heart failure, and severe anemia)</li> <li>Endocrine (hypo- or hyperglycemia, hypothyroidism)</li> </ul>
<p>Psychophysiological (5%)</p> <ul style="list-style-type: none"> <li>Anxiety with hyperventilation</li> </ul>
<p>Adverse Drug Effects (30%)</p> <p>Over 150 drugs have &gt;3% incidence of dizziness and vertigo, but those listed below are the major drug types.</p> <p>Vestibulotoxic drugs that cause permanent vestibular hair cell damage</p> <ul style="list-style-type: none"> <li><b>Aminoglycoside antibiotics</b> (<b>gentamycin</b> and kanamycin)</li> <li>Cancer chemotherapeutics (cisplatin and chlorambucil)</li> </ul> <p>Central nervous system drugs</p> <ul style="list-style-type: none"> <li><b>Sedatives</b> (benzodiazepines and sleeping pills)</li> <li>Psychoactive (phenothiazines, lithium, and tricyclics)</li> <li>Anticonvulsants (phenytoin and carbamazepine)</li> </ul> <p>Circulatory drugs</p> <ul style="list-style-type: none"> <li><b>Antihypertensives</b> (prazosin, ganglionic blockers, and β-blockers)</li> <li>Vasodilators (isosorbide and nitroglycerin)</li> <li>Antiarrhythmics (mexiletine, flecainide, and amiodarone)</li> <li>Loop diuretics (furosemide and ethacrinic acid)</li> </ul> <p>Herbal medicines</p> <ul style="list-style-type: none"> <li>Dizziness is a side effect of many herbs</li> </ul>

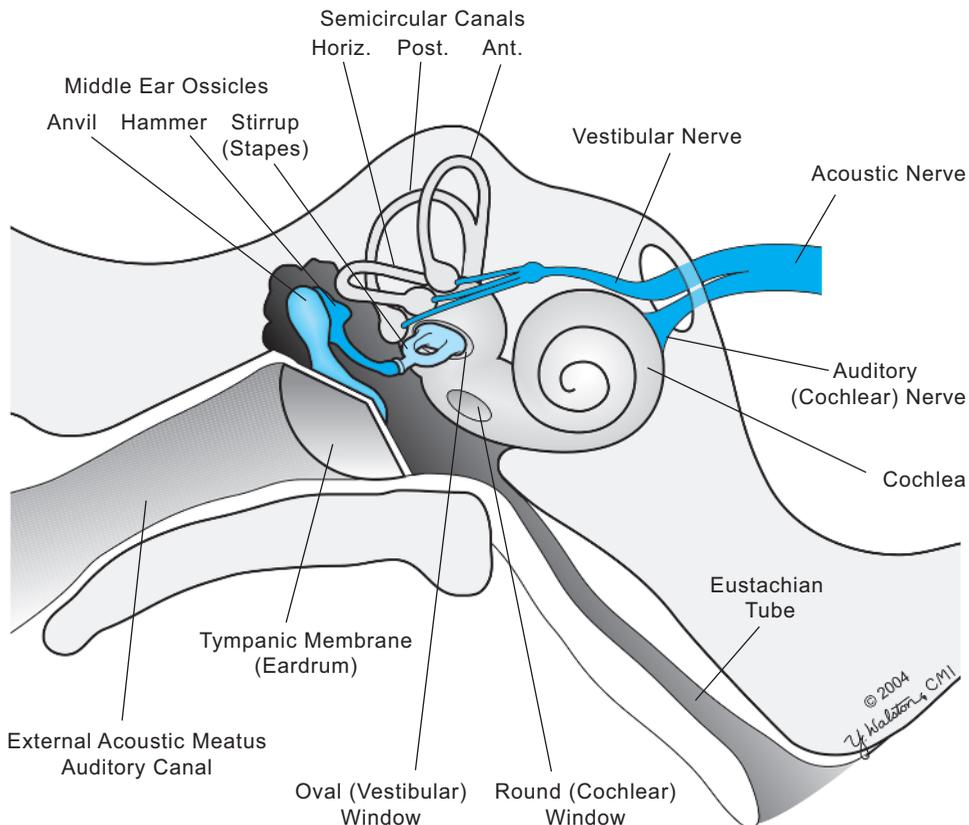
\*(%) refers to the approximate distribution of causes. **Bold** type refers to the most common cause in each category.

**Table 21-2** *Components of Normal Balance*

<b>Vestibular System</b>
Detects changes in gravity and adjusts body posture Maintains eye steadiness during head movement
<b>Proprioceptive System</b>
Knowledge of position of feet Detection of leg and foot movement (sway)
<b>Visual System</b>
Detection of head movement from horizon Feedback (“retinal slip”) information on integrity of vestibuloocular reflex
<b>Vestibular Nuclei in Brainstem and Cerebellum</b>
Integrates signals from vestibular, visual, and proprioceptive systems, sending information to the semicircular canals, eye muscles, and cerebral cortex to make appropriate changes in posture and eye movements.

vestibular nuclei regarding the integrity of the vestibuloocular reflex. The visual system is comprised of eyes, optic nerves, lateral geniculate nuclei, optic radiations, visual cortexes, and pathways from the lateral geniculate bodies and occipital cortex to vestibular nuclei. The visual system seldom causes primary dizziness. However, it is the major compensating system when other sensory systems are impaired. As such, patients commonly have good balance during the day but feel off balance and dizzy and fall at night when they have diminished vision.

The proprioceptive system delivers knowledge of foot position, detecting and compensating for leg and foot movement (sway). Joint position sensors located in the feet transmit changes in foot position via small myelinated peripheral nerves to the spinal cord. Information then rises to the vestibular nuclei via the posterior columns. Nerve impulses sent from joint position sensors in the feet are important for maintaining balance while standing and walking. Dysfunction of this system



**Figure 21-1** *Anatomy of the inner ear.*

does not lead to vertigo, but rather to a feeling of dizziness and being off balance (dysequilibrium) when standing and walking, which improves with lying down or sitting.

In summary, vestibular nuclei integrate signals from the vestibular, visual, and proprioceptive systems to trigger appropriate changes in posture to maintain balance and to alter eye position in order to keep the world steady during head movement. Paired vestibular nuclei in dorsal lateral medulla, as well as the flocculus and nodulus of the cerebellum, receive and integrate afferent sensory signals. Efferent signals travel via the medial and lateral vestibulospinal tracts to anterior horn neurons of antigravity muscles and to the sensorimotor cortex for conscious knowledge of body position and balance.

*Dizziness and vertigo are symptoms, not diseases.* The key to diagnosis is to determine which system(s) is responsible for the symptoms. The history, associated symptoms, and physical exam lead to the involved system (Table 21-3). If the vestibular system is involved, additional localization questions include: does the problem lie in the vestibuloocular reflex or vestibulospinal system, and is the dysfunction peripheral in the end organs (common) or central in the brainstem or cerebellum (uncommon)?

Frequently the history and exam are sufficient to establish the cause of the vestibular dysfunction. However, laboratory tests and neuroimaging may be helpful in some circumstances. Neuroimaging is not capable of demonstrating inner-ear membranous structures such as cristae or macula and is of little value for many primary vestibular diseases. However, thin CT sections through the temporal bones can identify a temporal bone fracture, tumor, or infection that damaged the inner ear. MRI can identify middle-ear infections, tumors including an acoustic neuroma, masses involving the cerebellopontine angle, and structural damage to the brainstem or cerebellum. Electronystagmography (ENG) records eye movements and nystagmus in response to a variety of maneuvers similar to those done in the office (Table 21-3). ENG also determines the integrity of the horizontal semicircular canal (but not other canals, utricle, or saccule) following irrigation of the external auditory canal with cool and warm water. ENG helps when one wants to determine if the vestibular dysfunction is bilateral, as in drug toxicity and hereditary diseases, or unilateral, as in vestibular

neuritis, Meniere's disease, and temporal bone destruction. Examination of CSF is seldom helpful unless a meningeal tumor or infection is suspected.

## Principles of Vertigo Management

Vertigo is a frightening experience often associated with marked nausea and vomiting. Reassurance and simple explanations often relieve much of the anxiety. The intensity of vertigo can be lessened with several medications. Diazepam administered intravenously usually stops severe symptoms. Promethazine given intravenously, rectally, or orally is effective in reducing the vertigo and nausea but is sedating. Meclizine offers minimal benefit.

Symptomatic treatment should be given for acute severe vertigo until the severe symptoms subside. Chronic administration of these drugs for mild vertigo may actually delay natural recovery and is especially sedating in the elderly. Patients with brief recurrent vertigo episodes seldom benefit from drugs. Patients with dizziness from proprioceptive, visual, or metabolic brainstem causes are not helped by antivertigo medications. Simply treating the vertigo symptom is insufficient; specific treatment should also be directed toward the etiology of the dizziness.

## Benign Paroxysmal Positional Vertigo

### Introduction

Benign paroxysmal positional vertigo (BPPV) or benign positional vertigo is the most common type of vertigo. Overall the incidence is 60/100,000 individuals per year, but the incidence rises to 120/100,000 per year in individuals over age 50 years. Most cases develop from peripheral SCC dysfunction, but a few are of central brainstem origin.

### Pathophysiology

The signs and symptoms of BPPV are due to abnormal movements of endolymphatic fluid in a SCC due to the presence of agglomerated debris. In most cases, the debris is otoconia breaking loose from the macula of the utricle. Gravity causes loose otoconia to fall downward into the posterior

**Table 21-3 Key Elements of the Office Evaluation of Dizziness or Vertigo**

<b>History</b>
Dizziness or vertigo Constant or intermittent Duration of dizziness (seconds, minutes, hours, days, weeks) Circumstances of onset (e.g., head trauma, infection, new drug usage, etc.) Triggers or exacerbating factors (head movement in particular direction, diabetic missing meals, getting out of bed, etc.) Course of vertigo improving, stable, or worsening Syncope (if yes, problem is not dizziness or vertigo)
<b>Associated Diseases, Signs, and Symptoms</b>
New hearing loss or tinnitus—vestibular Diplopia, new glasses, or cataracts—ocular Pain, numbness or paresthesias in feet, or bilateral leg weakness—proprioceptive Facial weakness, numbness, stiff neck, unequal pupils, or diplopia—brainstem or structural Diabetes mellitus, hypothyroidism, or cardiovascular disease—brainstem or metabolic
<b>Exam</b>
<b>Vestibuloocular system</b> Vestibuloocular reflex test: subject looks at distant target while slowly rotating the head horizontally or vertically. Abnormal result is when target moves and examiner sees late saccades to catch up with target. Head shaking test: subject rapidly rotates head horizontally (like saying “no”) for 10 cycles and then looks forward. Abnormal result is horizontal nystagmus present after stopping head shaking, and dizziness. Hallpike maneuver: Sit patient on exam table with back toward the end. Turn head 45° laterally and rapidly lay patient down with head hanging below the table for 30 seconds. Abnormal result is presence of directional-rotary nystagmus often after a short delay, with subject reproducing dizziness symptoms (Figure 21-3).
<b>Vestibulospinal system</b> Tandem gait test: subject walks a straight line with feet in front of each other. Abnormal result is when patient sways and side steps. Normal test suggests system is intact, but abnormal test has many causes, including orthopedic leg problems or proprioceptive or cerebellar dysfunction. Romberg test: subject asked to stand with feet together with eyes open and closed. Abnormal result is when patient can stand with eyes open but not closed, and implies dysfunction in proprioceptive or vestibular system.
<b>Nystagmus (described in direction of the fast phase)</b> Slow phase derives from vestibular activity and fast phase from cerebral cortex action to correct slow phase Nystagmus from vestibular end organ dysfunction is horizontal or direction-rotary, occurring in mid-position or 45° off center that is worsened by removal of fixation (such as by Frenzel +30 lenses). Nystagmus from central vestibular cause is purely rotary or purely vertical, long lasting, and independent of fixation. Gaze-evoked nystagmus is symmetrical, high-frequency, and low-amplitude horizontal nystagmus seen at end of far lateral gaze in both directions and is usually due to drugs such as alcohol, benzodiazepine, phenytoin, and sedatives.
<b>Hearing tests</b> Inspection of the external auditory canal with otoscope Ability to hear whispers or finger rubs in each ear and hear low frequencies such as 128-Hz tuning fork If hearing loss, determine if sensorineural (air conduction greater than bone conduction) or middle-ear conductive (bone conduction greater than air conduction)
<b>Proprioceptive system</b> Position and vibration sensitivity in feet Romberg test and tandem gait
<b>Visual system</b> Extraocular muscle exam for diplopia Simple visual acuity Fundoscopic exam for cataracts
<b>Brainstem and cerebellum</b> Cranial nerve exam (especially CNs V, VII, and IX)
<b>Cardiovascular</b> Heart rate and rhythm and presence of murmurs Lying and standing blood pressure
<b>Pulmonary</b> Respiratory rate resting and with exercise Auscultation of lungs

SCC (Figure 21-2). With rotation of the head in a vertical plane, the debris in one SCC briefly alters the dynamics of the vestibulocular in 1 SCC compared with the opposite side, causing transient vertigo.

**Major Clinical Features**

Most patients experience transient vertigo lasting less than 15 seconds when rotating their head upward (e.g., to place an object on a shelf) or downward (e.g., to tie their shoes). The sensation is unexpected and often disconcerting to the patient. There is no associated nausea, vomiting, hearing loss, tinnitus, or other neurologic signs. Attacks occur 1 to 5 times per day. If the maneuver that precipitated the episode is repeated several times, the vertigo fatigues, becoming less intense and shorter in duration, and then enters a refractory period for hours when the maneuver does not trigger dizziness. About 20% of cases follow minor head trauma, but most have no recognized precipitating factor.

Between attacks, the patient is asymptomatic and has normal balance and coordination. The Hallpike

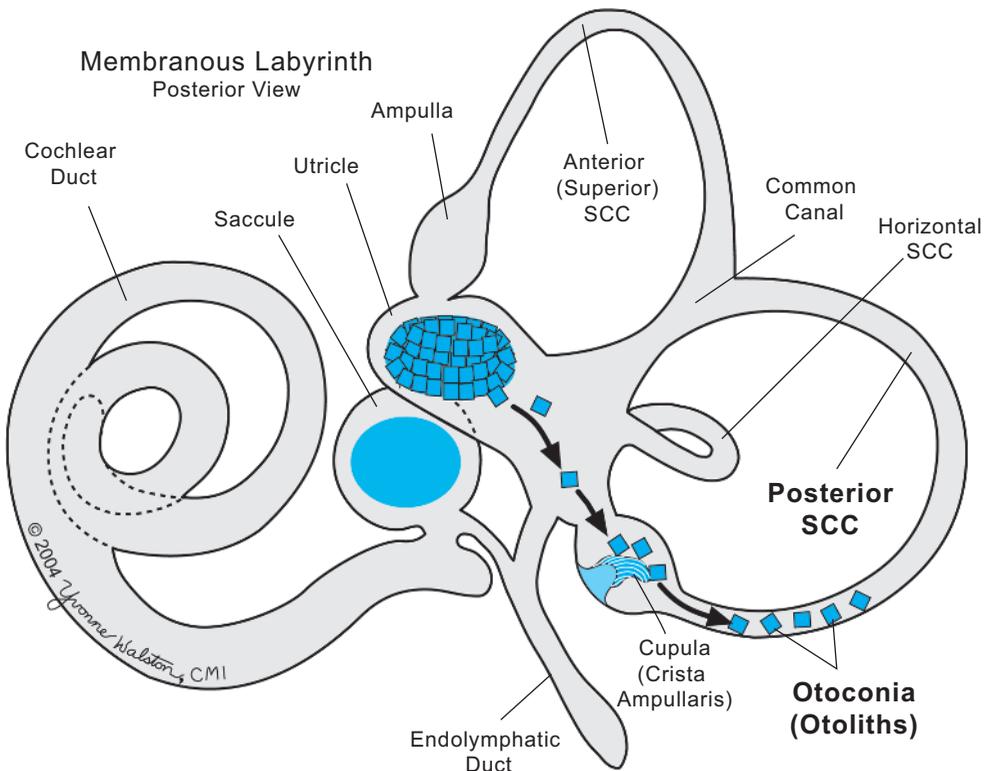
or Dix–Hallpike maneuver, performed in the office, can often trigger a patient’s vertigo (Figure 21-3, Table 21-3). The maneuver should reproduce the patient’s vertigo symptoms. The examiner looks for directional-rotary nystagmus to appear 1 to 5 seconds after the patient’s head is hanging below the table. The diagnosis is made based on a characteristic history and a positive Hallpike maneuver.

**Major Laboratory Findings**

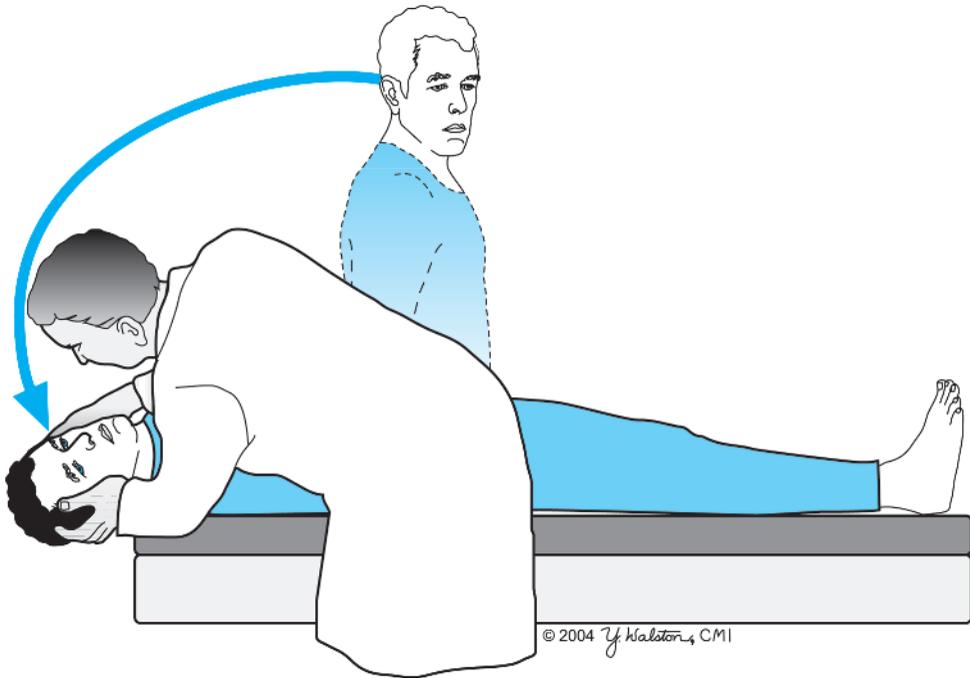
Neuroimaging and ENG tests are not helpful and are normal.

**Principles of Management and Prognosis**

Most episodes of BPPV spontaneous resolve within 1–2 months but a few can persist for prolonged periods. In over two-thirds of patients, BPPV can be terminated or greatly improved by the Epley maneuver (Figure 21-4) or otoconia-repositioning maneuver. In this maneuver, the posterior SCC canal debris moves by gravity around the SCC to



**Figure 21-2** Benign paroxysmal positional vertigo.



**Figure 21-3** Hallpike maneuver.

deposit back in the utricle where it is then absorbed. This is accomplished by repeating the maneuver with the ear side down that triggered the vertigo. Over a period of 2 minutes, the head is held in this position, then slowly rotated to midline, then rotated to the opposite side, and finally the patient is rotated to a sitting position. The patient sleeps on several pillows that night to prevent debris from falling back into the canal. The Epley maneuver eliminates or reduces BPPV over 75% of the time.

## Meniere's Disease

### Introduction

Meniere's disease, or endolymphatic hydrops, is less common than BPPV but more incapacitating. The yearly incidence varies from 10 to 150 cases per 100,000 individuals depending on the definition used. The illness affects both sexes and most ages, with peak age from 40 to 60 years.

### Pathophysiology

Temporal bone studies demonstrate characteristic endolymphatic hydrops with pathologic expan-

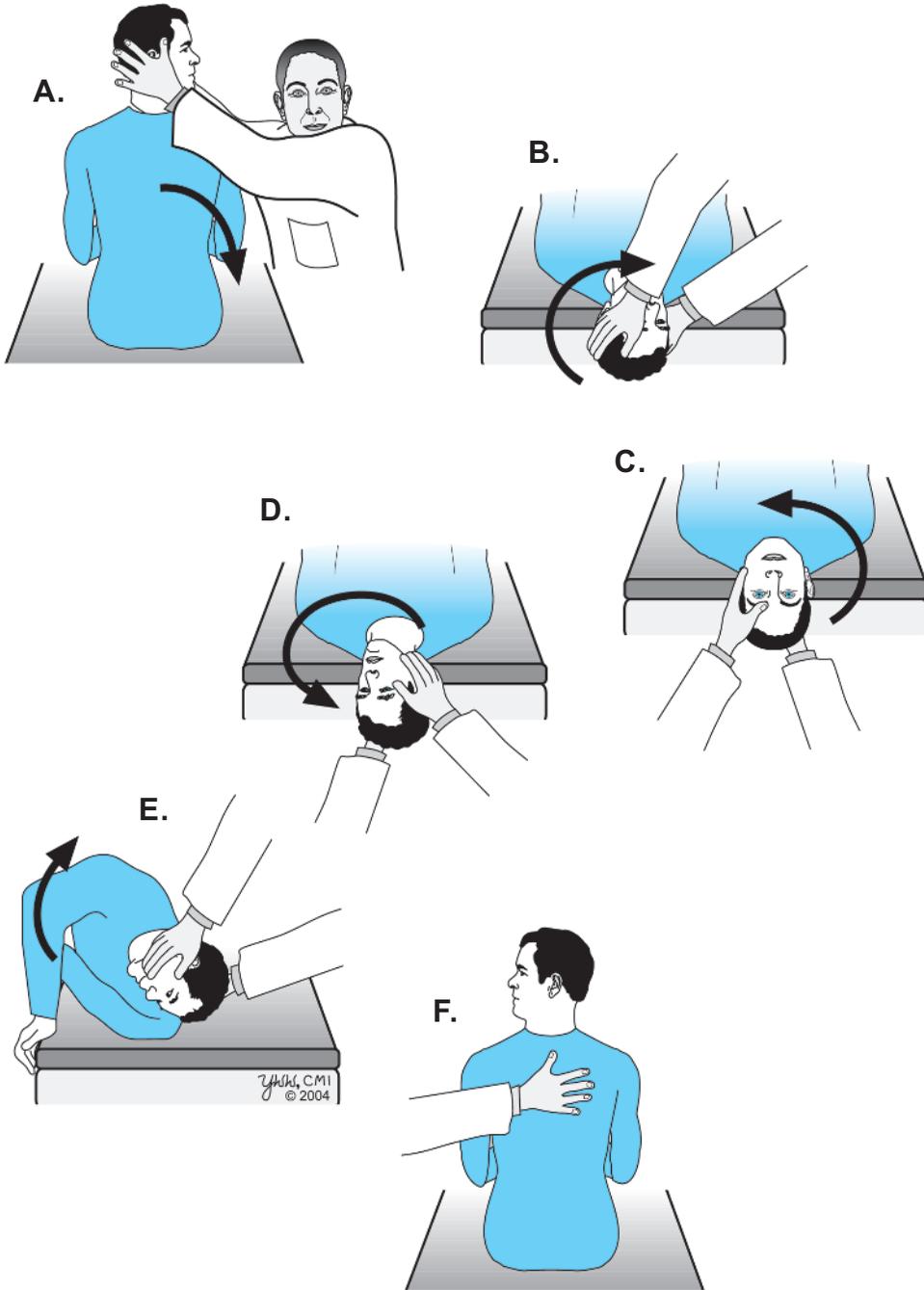
sion of endolymphatic fluid at the expense of the perilymphatic system. Secondary endolymphatic membrane ballooning and distortions develop in the cochlea, utricle, and saccule. Evidence of rupture with healing of endolymphatic membranes is common. There is variable damage either to cochlear or vestibular hair cells depending on the duration of the disease.

Acute attacks are thought to occur when an endolymphatic membrane rupture occurs transiently, allowing potassium-rich endolymph and potassium-depleted perilymph to mix. The resulting abnormal stimulation of vestibular and cochlear axons leads to permanent hearing and vestibular function loss over time.

The etiology is unknown in over 90%. The remaining cases appear as delayed consequences of otitic syphilis, mumps labyrinthitis, head trauma, or meningitis. Of these patients, 10% have a family history of Meniere's disease.

### Major Clinical Features

Abrupt attacks of vertigo develop without warning or are preceded by an aura of increasing tinnitus, fullness in the ear, and diminished hearing on that



**Figure 2-4** Epley maneuver. Hold each step for 30 seconds.

side. No triggers are known. The vertigo, characterized as a horizontal spinning sensation, is accompanied by horizontal nystagmus, nausea, and often vomiting. The severity of vertigo varies by attack but is often severe enough to prevent

walking. Associated tinnitus (roaring or whistling sound) and diminished or muffled hearing affect the involved ear. Attacks usually last up to several hours, the patient may feel exhausted and unsteady for 1 day. The typical frequency of

attacks is 1 per month, with a range of 2 per week to 2 per year. The patient slowly and progressively loses hearing in the involved ear.

### Major Laboratory Findings

The progressive hearing loss begins with low frequencies (peak loss at 250–500 Hz) such that speech discrimination is affected early. As the disease progresses, all frequencies are lost. Finding low-frequency hearing loss is helpful, as most cases of acquired sensorineural hearing loss, such as hearing loss in the elderly (presbycusis), involve high frequencies. In over 50% of patients, caloric testing demonstrates a diminished or absent caloric response in the involved ear. Neuroimaging and CSF are normal in idiopathic cases.

### Principles of Management and Prognosis

There is no cure for the disease. Acute vertiginous attacks are difficult to symptomatically treat, as nausea and vomiting prevent use of oral medications and the vertigo often ends in  $1/2$  to 2 hours. Rectal medications, such as promethazine suppositories, lessen the vertigo and nausea. Since the clinical course and frequency of attacks are variable, determination of effective drugs to reduce the frequency of attacks has been difficult. The most commonly administered treatments are aimed at reducing production or enhancing absorption of

endolymph and include low salt diets and daily diuretics (hydrochlorothiazide or acetazolamide). In patients with frequent severe attacks who fail medical treatment, gentamycin locally instilled in the middle or inner ear has been successful in destroying vestibular hair cells, with reduction of attack severity, but at the price of variable loss of hearing in that ear. Surgical approaches to shunt endolymph or destroy vestibular nerves are unproven.

Spontaneous vertigo attacks usually subside over 5 to 10 years, when the disease progresses to the point where the patient is deaf and has no caloric response. Unfortunately, 15% of patients develop Meniere's disease in the opposite ear.

### RECOMMENDED READING

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- Baloh R. *Dizziness, Hearing Loss, and Tinnitus*. Philadelphia: FA Davis; 1998. (*Excellent straightforward book on causes of vertigo.*)
- Furman JM, Cass SP. Benign Paroxysmal Positional Vertigo. *N Engl J Med* 1999;341:1590-1596. (*Excellent review of this syndrome and the Epley maneuver.*)
- Paparella MM, Djalilian HR. Etiology, pathophysiology of symptoms, and pathogenesis of Meniere's disease. *Otolaryngol Clin North Am* 2002;35:529-545. (*Entire issue devoted to reviews of Meniere's disease.*)

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# Glossary of Common Neurologic Terms

**Accommodation** Sensory nerves having dynamic firing rates that decline with time even though the stimulus is maintained. Changes in the eye that enable clear vision at various distances.

**Afferent pathway** Axons leading to the brain or spinal cord.

**Agnosia** Lack of knowledge and is synonymous with an impairment of recognition. An example is visual agnosia in which patient cannot arrive at the meaning of previously known nonverbal visual stimuli despite normal visual perception and alertness.

**Agraphia** Inability to recognize numbers/letters written on the palm or fingertips.

**Alexia** Acquired reading impairment that may be accompanied with writing deficits (alexia with agraphia) or without writing deficits (alexia without agraphia).

**Allodynia** Non-painful cutaneous stimuli causing pain.

**Amaurosis fugax** Transient monocular blindness. This usually comes from an internal carotid artery embolus temporarily occluding the ophthalmic artery.

**Amnesia** Partial or complete loss of the ability to learn new information or to retrieve previously acquired knowledge.

**Amyotrophy** Wasting of muscles usually from denervation.

**Anal reflex** Reflexive contraction of anal sphincter upon perianal sensory stimulation.

**Aneurysm** Abnormal dilatation or bulging of an intracranial artery wall, usually at bifurcations of the Circle of Willis.

**Anisocoria** Unequal pupil size.

**Ankle jerk** Deep tendon reflex (Achilles reflex) elicited by striking the Achilles tendon at the ankle resulting in foot plantar flexion.

**Anterior horn** Gray matter in the ventral spinal cord that contains neurons including anterior horn cells (lower motor neurons).

**Anterior root** Segment of motor nerves composed of anterior horn neurons exiting the ventral spinal cord to where they join the mixed peripheral nerve.

**Anton's syndrome** Lesions involving the occipital and parietal lobes that produce blindness or a homonymous hemianopia that is denied by the patient.

**Aphasia** Disorder of expression or comprehension of spoken language due to dysfunction of language centers in dominant cerebral cortex or thalamus.

**Apoptosis** Genetically programmed neuronal cell death that may be normal or abnormal.

**Apraxia** Inability to perform a learned act, despite demonstrated ability to perform com-

- ponents of the act usually due to dysfunction of a parietal lobe.
- Arteriovenous malformation (AVM)** Abnormal blood vessel complex consisting of arteries, veins, and capillaries located in the brain or spinal cord that often hemorrhage.
- Arteritis** Inflammation of walls of arteries.
- Astereognosis** The inability to distinguish and recognize small objects based on size, shape, and texture when placed in the hand that has normal primary tactile sensory input.
- Ataxia** Incoordination of limb or body movements, particularly gait, often due to impairment of cerebellar function.
- Athetosis** Involuntary movements characterized by slow, sinuous, twisting of arms, legs, or body.
- Atrophy** Wasting of muscle/s from disuse or denervation.
- Autism** Childhood illness affecting language and interpersonal relationships.
- Babinski sign** Extensor response of the great toe with fanning of the other toes in response to stimulus on sole of foot. The extensor plantar response is normal in infants to about 9 months, thereafter reflects damage to the corticospinal tract (upper motor neuron sign).
- Basal ganglia** Deep gray matter nuclei of the cerebral hemispheres comprising putamen, caudate, globus pallidus, subthalamic nucleus, substantia nigra, and often thalamus.
- Biceps reflex** Deep tendon reflex elicited by hitting the biceps tendon resulting in brief contraction of the biceps muscle.
- Brachioradialis reflex** Deep tendon reflex elicited by hitting the distal radius resulting in brief contraction of the brachioradialis muscle.
- Bradykinesia** or **Akinesia** Difficulty in moving despite intact motor nerves and normal muscles as seen in Parkinson's disease.
- Broca's aphasia** Motor speech disorder (expressive aphasia, nonfluent or anterior aphasia) due to dysfunction located in the dominant frontal lobe and characterized by effortful, sparse, agrammatic, halting, truncated speech with loss of normal language melody.
- Bruit** Sound due to turbulence of blood passing a narrow artery segment, often heard from the internal carotid artery in the neck.
- Bulbar** Refers to the medulla and pons of the lower brainstem.
- Calcarine cortex** Primary visual cortex located in the medial occipital lobe.
- Caloric test** Placement of warm or cool water in the external canal to evaluate eye movements from stimulation of the vestibulo-ocular reflex.
- Cauda equina** Lumbosacral nerve roots in the lumbar and sacral vertebral canal before the exit via neural foramina.
- Caudal** Lower in the neural axis compared with other structures of the same kind nearer the head.
- Charcot-Marie-Tooth disease** Dominant autosomal genetic disease affecting distal myelinated axons of limbs, especially legs producing distally symmetrical polyneuropathy.
- Cheyne-Stokes respirations** Regular cyclic oscillations of breathing between hyperpnea or over breathing and apnea.
- Chorea** Abnormal involuntary movements characterized by rapid flicks or jerks of limb, face, or trunk muscles.
- Chromatolysis** Disintegration of chromophilic substance or Nissl body from neuron when the axon is divided.
- Cogwheel rigidity** Ratchet-like increased resistance to passive movement (hypertonia) usually found at the wrists of patients with Parkinson's disease.
- Computerized tomography (CT)** Neuroimaging technique based on computer processing of data from differential attenuation of x-ray beam passing through tissue (often the skull & brain) that produces a series of slices through the tissue.
- Constructional apraxia** Disturbances in organizing parts of a complex object.
- Corticobulbar tract** Descending cortical motor tract traveling to a brainstem motor nucleus.
- Corticospinal tract** Descending cortical motor tract primarily from motor cortex that descends down the spinal cord to synapse at anterior horn cells or adjacent interneurons.

- Countercoup** Injury to brain on opposite side as head trauma.
- Coup** Injury occurring to brain on same side as head trauma.
- Decerebrate posture** Both arms and legs are extended, especially when painful stimuli are administered usually due to a lesion that separates upper from lower brainstem.
- Decorticate posture** Flexion of one or both arms and extension of ipsilateral or both legs due to lesion that isolates brainstem from contralateral or bilateral cortical influences.
- Deep tendon reflexes** (DTR) Term used to describe a monosynaptic stretch reflex elicited by tapping a tendon with resulting muscle contraction.
- Demyelination** Primarily loss of the axon nerve sheath in the peripheral or central nervous system with relative sparing of the underlying axon. Segmental demyelination implies that the myelin loss is patchy along the nerve leaving part of the axon with intact myelin.
- Dizziness** General term to describe sensation of light-headedness or feeling off balance.
- Doll's eyes maneuver** Vestibulo-ocular reflex that is performed usually in comatose patient where the head is rotated laterally but the eyes remain stationary and do not move with head.
- Dominance** Term that refers to cerebral hemisphere that controls language and principle limb involved in writing, eating, and throwing.
- Dorsal column nuclei** Nucleus gracilis and cuneatus in the caudal medulla that contain 2<sup>nd</sup> order neuronal cell bodies for the dorsal columns in the spinal cord and usually conduct position sense, vibration, and touch sensations.
- Dorsal horn** Dorsal (posterior) aspect of the spinal cord gray matter that contains neurons associated with peripheral afferent sensory fibers.
- Dorsal root** Part of the peripheral afferent sensory nerve between the dorsal root ganglia and the dorsal horn of the spinal cord.
- Dorsal root ganglia** Cluster of 1<sup>st</sup> order peripheral afferent sensory neuron cell bodies located at each segmental level near vertebral bodies.
- Dressing apraxia** Lesions only involving the non-dominant parietal lobe that produce neglect on one side of the body in dressing and grooming.
- Dysarthria** Impaired articulation of speech that sounds like “speaking with rocks in your mouth.”
- Dyskinesia** Several involuntary movements of limbs or face that include chorea, athetosis, tics, and dystonia.
- Dysmetria** Limb ataxia in directed movement that misses the target.
- Dysphagia** Impairment of swallowing.
- Dysphonia** Difficulty in speaking, often with a low speech volume.
- Dystonia** Strong, sustained, and slow contractions of muscle groups that cause twisting or writhing of a limb or the entire body. The contractions are often painful and may appear disfiguring. The dystonia lasts seconds to minutes and occasionally hours producing a dystonic posture.
- Edema** Excess water in the brain from swelling of cell bodies (cytotoxic) or increased fluid in extracellular spaces (vasogenic).
- Efferent pathway** Axons leading away from the brain or spinal cord.
- Electroencephalograph** Instrument for recording minute electrical currents developed in the brain by means of electrodes attached to the scalp.
- Electronystagmograph** Instrument for recording electrical signals generated by eye movements or nystagmus during tests to evaluate patients with vertigo.
- Epilepsy** Illness resulting from repetitive seizures due to abnormal brain electrical activity that is often subdivided into specific seizure types (e.g., generalized tonic-clonic).
- Epley maneuver** In patients with benign paroxysmal positional vertigo, a variation of the Hallpike maneuver is performed to roll loose otoconia around the posterior semicircular canal eliminating the recurrent brief vertigo spells.

**Extraocular movements** Eye movements due to contraction of extraocular eye muscles rather than muscles that govern the iris and lens.

**Falx cerebri** Rigid dural fold in midsagittal plane that separates the two hemispheres.

**Fasciculation** Contraction of fascicle (group) of muscle fibers innervated by single nerve from one anterior horn neuron that produces visible intermittent spontaneous twitching of part of a muscle but does not move the body part.

**Fibrillation** Spontaneous contraction (invisible to the eye but detected by EMG) of individual denervated muscle fibers no longer under the control of a motor nerve.

**Flaccid** Limp muscle that has no muscle tone.

**Foramen magnum** Large opening at base of skull where spinal cord and brainstem join.

**Fovea** Central part of macula of retina related to sharpest vision for reading.

**Frenzel glasses** Strong positive lenses that inhibit patients from seeing clearly enough to fixate but allow the examiner to see the eye. Glasses used to detect nystagmus.

**Gadolinium** Rare earth compound given intravenously before MRI to detect brain areas that have a broken blood-brain barrier (such as at tumors).

**Ganglia** Clusters of neurons all having similar function, such as dorsal root ganglia.

**Gerstmann's syndrome** The inability to designate or name the different fingers of the two hands, confusion of the right and left sides of the body and inability to calculate or to write.

**Glasgow coma scale** Simple scoring system of unconscious patients based on eye opening, motor response, and verbal response that is useful for prognosis.

**Glia** Term for supporting cells of CNS that includes astrocytes and oligodendroglia.

**Glioma** Term used for CNS tumors of astrocyte or oligodendrocyte lineage.

**Global aphasia** Acquired loss of ability to comprehend or produce verbal messages.

**Gower's maneuver** Seen in muscular dystrophy where an individual with weak proximal leg

muscles places his hands on the knees and climbs up his thighs to stand.

**Grasp reflex** Involuntary grasping of the hand when the palm is stimulated. This is normal in babies but abnormal in older children and adults and is often associated with diffuse frontal lobe damage.

**Gray matter** Term that refers to gray color of part of CNS that contains neurons rather than white matter that contains mainly axons and myelin sheaths.

**Hallpike maneuver** A test to detect positional nystagmus performed by laying a patient down with their head hanging below the table.

**Hammer toes** Cocking up of toes like gun hammers often due to a distal sensorimotor polyneuropathy causing atrophy and weakness of intrinsic flexor toe muscles with overriding pull of more proximal extensor toe muscles.

**Hemianopia** Refers to loss of vision in half the visual field in the vertical plane. If both eyes are equally involved, it is called homonymous hemianopia.

**Hemiparesis** Incomplete weakness involving one side of body.

**Horner's syndrome** Miosis, ptosis, and diminished sweating on the ipsilateral face due to lesion in the 3rd neuron pathway starting in hypothalamus and traveling to the brainstem, thoracic spinal cord, cervical sympathetic ganglion, and sympathetic nerves along the carotid and ophthalmic arteries.

**Hydrocephalus** Abnormal enlargement of one or more ventricles of the brain. Obstructive hydrocephalus is when there is obstruction of CSF flow in ventricular system or subarachnoid space. Hydrocephalus ex vacuo refers to passive ventricular enlargement from loss of surrounding white matter and neurons. Communicating hydrocephalus refers to nonobstructed pathway from spinal subarachnoid space to lateral ventricles.

**Hypertonia** Increased muscle tone or resistance produced by passive movement of a limb on a joint.

**Hypotonia** Decreased muscle tone or resistance produced by passive movement of a limb on a joint.

- Hypsarrhythmia** Random, high-voltage slow waves and spikes seen on EEG that vary from in time and location.
- Ice water caloric** Test used in comatose patients to determine whether the pathway from the vestibular inner ear to the 3rd and 6th cranial nerves is intact. When pathway is intact, ice water irrigated in one ear produces bilateral eye movement to the ipsilateral side.
- Infantile spasms** Brief, symmetric contractions of neck, trunk, and limb muscles seen in infants (also called salaam seizures).
- Ischemic penumbra** Area of brain around an acute stroke that immediately has insufficient blood flow to function but sufficient to prevent cell death and may or may not subsequently die.
- Jaw jerk** Corticobulbar reflex produced by tapping downward on the chin with resulting contraction of masseter muscles and upward jaw movement. When unusually brisk, the jaw jerk implies an upper motor neuron abnormality in corticobulbar tract to 5th cranial nerve nuclei.
- Kernicterus** Deposition of bile pigment in deep brain nuclei with neuronal degeneration from neonatal jaundice.
- Knee jerk (KJ)** The patellar reflex is a deep tendon reflex in which the patellar tendon is tapped causing a brief extension of the leg.
- Korsakoff's syndrome or psychosis** Loss of the ability to learn new memories with a tendency to fabricate answers. It is usually part of Wernicke-Korsakoff's encephalopathy from alcoholism.
- Lateral geniculate body (nucleus)** Thalamic nucleus that receives input from optic nerves and sends outward optic radiations to the occipital cortex and upper brainstem.
- Lateral medullary syndrome** Infarction of dorsolateral medulla and inferior cerebellum due to occlusion of posterior inferior cerebellar artery, a branch of the vertebral artery.
- Lenticular (lentiform) nucleus** Combination of the putamen and the globus pallidus.
- Leukomalacia** Abnormal softening of white matter areas.
- Lordosis** Curvature of the spinal column with a forward convexity.
- Lower motor neuron** Motor neurons in the anterior horn of the spinal cord or brainstem that directly innervate muscles.
- Lumbar puncture** Placement of a hollow needle with a stylet into the spinal canal in the lower lumbar space to withdraw cerebrospinal fluid or instill medications.
- Magnetic resonance imaging (MRI)** Use of changing magnetic fields to create brain images as brain slices in any plane.
- Meralgia paresthica** Sensory impairment and dyesthesias in the skin distribution of the lateral femoral cutaneous nerve of the thigh.
- Mesial temporal sclerosis** Progressive loss of neurons and gliosis in one hippocampus that often causes complex partial seizures.
- Miosis** Abnormal constriction of a pupil.
- Mononeuropathy** Lesion involving a single peripheral nerve.
- Mononeuropathy multiplex** Lesions involving more than one peripheral nerve.
- Myalgia** Muscle aches and pains that are not cramps.
- Myelin** Lipid-protein sheath that wraps some peripheral nerves that is made by Schwann cells and some central nerves that is made by oligodendroglia.
- Myeloradiculopathy** Disease process affecting the spinal cord, adjacent peripheral nerve roots, and nerves.
- Myoclonus** Rapid, brief muscle jerks involving specific muscles or the entire body that do not blend together and are shorter duration than chorea. Nocturnal myoclonus is the normal abrupt body jerks that occur when an individual is falling asleep. The electroencephalogram may or may not have spikes correlating with the myoclonus.
- Myopathy** General term implying disease of muscle from any cause.
- Myotonia** Abnormal sustained muscle contractions with slow relaxation that have a characteristic pattern on electromyogram.

- Neglect** Inability to attend normally to a portion of extrapersonal or intrapersonal space or both that cannot be explained by altered perception. In visual neglect, the patient ignores objects, persons, or movement in the left or right of the environment.
- Neuraxis** Longitudinal axis of the central nervous system that runs from the rostral forebrain to the caudal spinal cord.
- Neuronophagia** Destruction of neurons by phagocytic cells.
- Neuropathy** Term that describes disorders of peripheral nerves.
- Nocioceptive** Sensory receptors that respond to painful stimuli.
- Non-convulsive status epilepticus** Complex partial status epilepticus where the patient has constant confusion and impaired awareness but can move his limbs.
- Nystagmus** Oscillatory eye movements that may be physiologic (following spinning in a circle) or abnormal (from inner ear, brainstem, and cerebellar dysfunction).
- OD** Right eye.
- Ophthalmoplegia** Paralysis of eye movements.
- Oriented x 3** Oriented to person, place, and time in mental status testing.
- Orthostatic hypotension** Fall in blood pressure upon standing causing dizziness or even syncope.
- OS** Left eye.
- Otoconia** Tiny calcium carbonate crystals embedded in a gelatinous matrix above the macula of the utricle and saccule that move with gravity changes bending attached hair cells allowing detection of gravity.
- Otorrhea** CSF drainage from ear.
- Papilledema** Swelling of optic nerve disc from elevated intracranial pressure.
- Paraphasias** Mispronounced or inappropriately substituted words with semantic paraphasias being errors based on meanings of words (aunt for uncle) and literal paraphasias being errors based on sounds (hook for took).
- Paresthasias** Spontaneous firing of peripheral nerve fibers causing a tingling sensation.
- Paroxysmal** Sudden event, as in spikes on electroencephalogram.
- Past pointing** Repeated missing a target by going too far or off to one side when using a finger or toe with closed eyes that is due to dysfunction of the vestibular system or cerebellum.
- Patellar reflex** Knee jerk reflex is a deep tendon reflex in which the patellar tendon is tapped causing a brief extension of the leg.
- Peripheral nervous system (PNS)** All neural structures that lie outside the spinal cord and brainstem and includes motor, sensory, and autonomic nerves and their ganglia.
- PERRLA** Abbreviation for pupils equal, round, and reactive to light and accommodation.
- Phlebitis** Inflammation of veins.
- Phonophobia** Discomfort from noises that normally do not cause discomfort.
- Photophobia** Abnormal eye pain from bright lights.
- Polyneuropathy** Diffuse and symmetrical distal dysfunction of sensory, motor, and autonomic nerve axons that usually begins in the feet.
- Positron emission tomography (PET)** Imaging technique that detects emissions from injected radiolabeled compounds to create a quantifiable image of blood flow, glucose utilization, or location of specific ligands that attach to brain receptors, etc.
- Prefrontal lobe** Part of brain anterior to the motor and premotor cortex that is a multisensory association cortex.
- Prion** Abnormal protein configuration of a normal host protein that causes transmissible spongiform encephalopathies, like Creutzfeldt-Jakob disease.
- Proprioception** Sense of position of body part relative to fixed object like a floor that is both unconscious and conscious.
- Prosopagnosia** Inability to recognize familiar faces (**facial agnosia**).
- Pseudobulbar palsy** Syndrome that affects speech articulation, phonation, swallowing, and emotional lability due to bilateral dysfunction of corticobulbar tracts in the brainstem.

- Psychomotor retardation** Abnormal slowing of mental behavior and limb movements that is not due to mental retardation.
- Ptoxis** Abnormal drooping of one or both eyelids.
- Putamen** Part of basal ganglia. The caudate and putamen form the striatum and putamen and globus pallidus form the lentiform or lenticular nucleus.
- Quadrantanopia** Loss of vision in one quadrant of vision.
- Radiculopathy** Damage to a nerve root leaving the spinal cord that causes weakness, sensory loss or dysesthesias, and diminished reflex in corresponding myotome and dermatome.
- Ramsay Hunt syndrome** Acute facial weakness due to herpes-zoster virus reactivation from the geniculate ganglion.
- Rigidity** Constant resistance to muscle stretching in both flexors and extensors throughout range of motion due to the stretching force inducing some motor units to fire. In Parkinson's disease, rapid flexion and extension of wrist or elbow often elicits a ratchet-like feeling (**cogwheel rigidity**).
- Rinne test** Comparison of bone conduction (placing a vibrating tuning fork on the mastoid process) to air conduction in which air conduction normally is heard better.
- Rolandic fissure** Fissure that separates the motor cortex in the frontal lobe from the sensory cortex in the parietal lobe.
- Romberg sign** Ability to stand with feet together and eyes open and the inability to maintain posture with the eyes closed.
- Rooting reflex** Normal turning of infant's face and lips toward a nipple touching the cheek but abnormal "frontal release reflex" when seen in adults upon touching the cheek.
- Rostral** Direction or position of neuroaxis towards the forebrain and away from the caudal spinal cord.
- Saccadic eye movement** Fast eye movement, voluntary or reflex, usually accomplishing foveal fixation.
- Salaam seizures** Brief, symmetric contractions of neck, trunk, and limb muscles seen in infants (also called infantile spasms).
- Saltatory conduction** Nerve action potential that moves down a myelinated nerve by jumping from node of Ranvier to node of Ranvier, increasing conduction velocity to as fast as 80 meters/second.
- Sciatica** Term for radiating pain down a leg from damage to one or more lumbosacral nerve roots that form the sciatic nerve.
- Semicircular canals** Three canals at right angles to each other and located in the temporal bone detect angular acceleration and serve to keep eyes steady during head movement.
- Shunt** Tubing used to move cerebrospinal fluid that is blocked along its pathway (usually a ventricle) to the abdomen or jugular vein where it can be absorbed.
- Single photon emission computed tomography (SPECT)** Imaging system that is similar but cheaper than positron emission tomography that qualitatively determines regional blood flow or brain metabolism relative to other brain areas.
- Skew deviation of vision** Vertical and slightly horizontal (diagonal) double vision that is the same in all fields of gaze due to a brainstem lesion.
- Snout reflex** Pouting of lips following tapping the lips.
- Spasticity** Condition resulting from damage to the corticospinal tract in which at-rest muscles are in midposition and limbs held in a characteristic flexed posture. Rapid passive limb movement initially produces little resistance but then quickly has increasing muscular resistance to a point when the resistance suddenly disappears ("clasp-knife" phenomena).
- Stenosis** Narrowing of lumen of artery or spinal canal.
- Strabismus** Lack of eye alignment such that the two visual axes assume positions relative to each other different from that required by the physiologic task.

- Straight leg raise test** Test for lumbar radiculopathy in which passive elevation of a straightened leg produces pain in the lower back.
- Striate cortex** Primary visual cortex.
- Striatum** Combination of the caudate nucleus and the putamen.
- Subfalcine space** Space beneath the falx in which the cingulate gyrus can herniate from increased intracranial pressure.
- Suck reflex** Normal sucking response of infants when touching the lips but abnormal “frontal-release” reflex in adults when touching the lips elicits a sucking response.
- Sylvian fissure** Major horizontal fissure that separates the temporal lobe from adjacent parts of the frontal and parietal lobes.
- Tandem gait** Walking heel to toe in a straight line.
- Tics** Abrupt, transient, repetitive, stereotypical movements of face and limbs or vocalizations that may be briefly voluntarily suppressed but is often then followed by a burst of tics when the suppression is removed.
- Tonsillar herniation** Downward movement of cerebellar tonsils into the foramen magnum in response to increased intracranial pressure from localized mass in the posterior fossa.
- Tonsils** Most inferior part of the midline cerebellum.
- Transient ischemic attack** Focal neurologic signs from transient occlusion of a cerebral artery that usually last less than an hour but always less than 24 hours.
- Triceps jerk** Deep tendon reflex elicited by tapping the triceps tendon above the back of the elbow.
- Uncal herniation** Movement of the uncal gyrus of the medial temporal lobe under the tentorial notch in response to mass in the temporal-frontal lobes producing increased intracranial pressure.
- Upper motor neuron** Neurons in the upper brain that synapse with lower motor neurons in the brainstem or spinal cord.
- Utricle** Part of the inner ear that detects gravity.
- Valsalva maneuver** Increase in intrapulmonic pressure by forcible expiration against a closed glottis.
- Ventricles** Four cerebrospinal fluid-filled cavities in the brain (lateral ventricles, third ventricle and fourth ventricle) along the cerebrospinal fluid pathway.
- Vermis** Midline part of the cerebellum that participates in truncal balance and gait.
- Vertigo** Illusion of abnormal spinning movement by the individual or his environment.
- Watershed brain territory** Cerebral cortex located between the distal ends of the middle and posterior cerebral arteries (parietal lobe) and middle and anterior cerebral arteries (anterior frontal lobe) that are damaged when hypoperfusion of the brain occurs.
- Wernicke’s aphasia** Language disorder in which there is loss of ability to comprehend verbal or written communications and ability to speak in fluid sentences with normal melody that make no sense.
- White matter** Central nervous tissue that contains mainly myelinated (white appearing) nerve fibers, but not their neuronal cell bodies.
- Xanthochromia** Yellow color of CSF supernatant that comes from lysed RBCs, bilirubin, or very elevated CSF protein concentration.

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