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# Disorders of Equilibrium

### KEY CONCEPTS

- 1 Disorders of equilibrium can be produced by disorders that affect vestibular pathways, the cerebellum, or sensory pathways in the spinal cord or peripheral nerves.
- 2 Disorders of equilibrium present with one or both of two cardinal symptoms: *vertigo*—an illusion of bodily or environmental movement, or *ataxia*—incoordination of limbs or gait.
- 3 Cerebellar hemorrhage and infarction produce disorders of equilibrium that require urgent diagnosis, because surgical evacuation of the hematoma or infarct can prevent death from brainstem compression.

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### APPROACH TO DIAGNOSIS

**Equilibrium** is the ability to maintain orientation of the body and its parts in relation to external space. It depends on continuous visual, labyrinthine, and somatosensory (proprioceptive) input and its integration in the brainstem and cerebellum.

- 1 Disorders of equilibrium result from diseases that affect central or peripheral vestibular pathways, the cerebellum, or sensory pathways involved in proprioception.
- 2 Such disorders usually present with one of two clinical problems: **vertigo** or **ataxia**.

#### 1. Vertigo

Vertigo is the illusion of movement of the body or the environment. It may be associated with other symptoms, such as **impulsion** (a sensation that the body is being hurled or pulled in space), **oscillopsia** (a visual illusion of moving back and forth), nausea, vomiting, or gait ataxia.

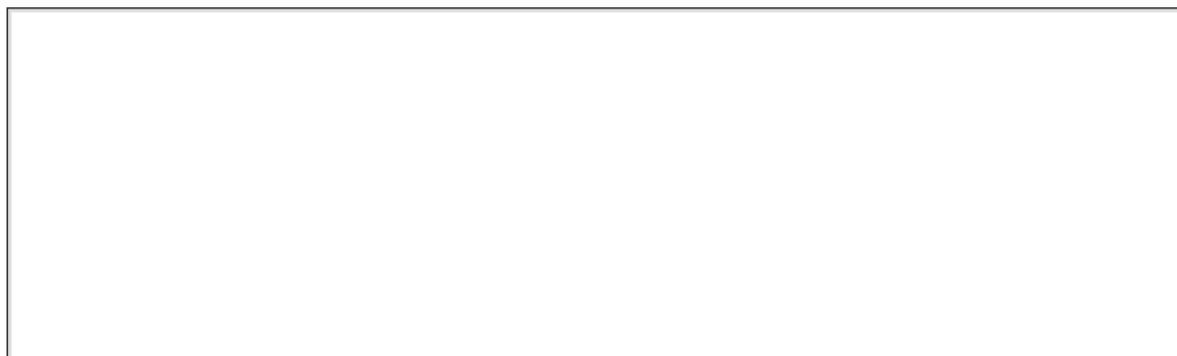
#### Distinction Between Vertigo & Other Symptoms

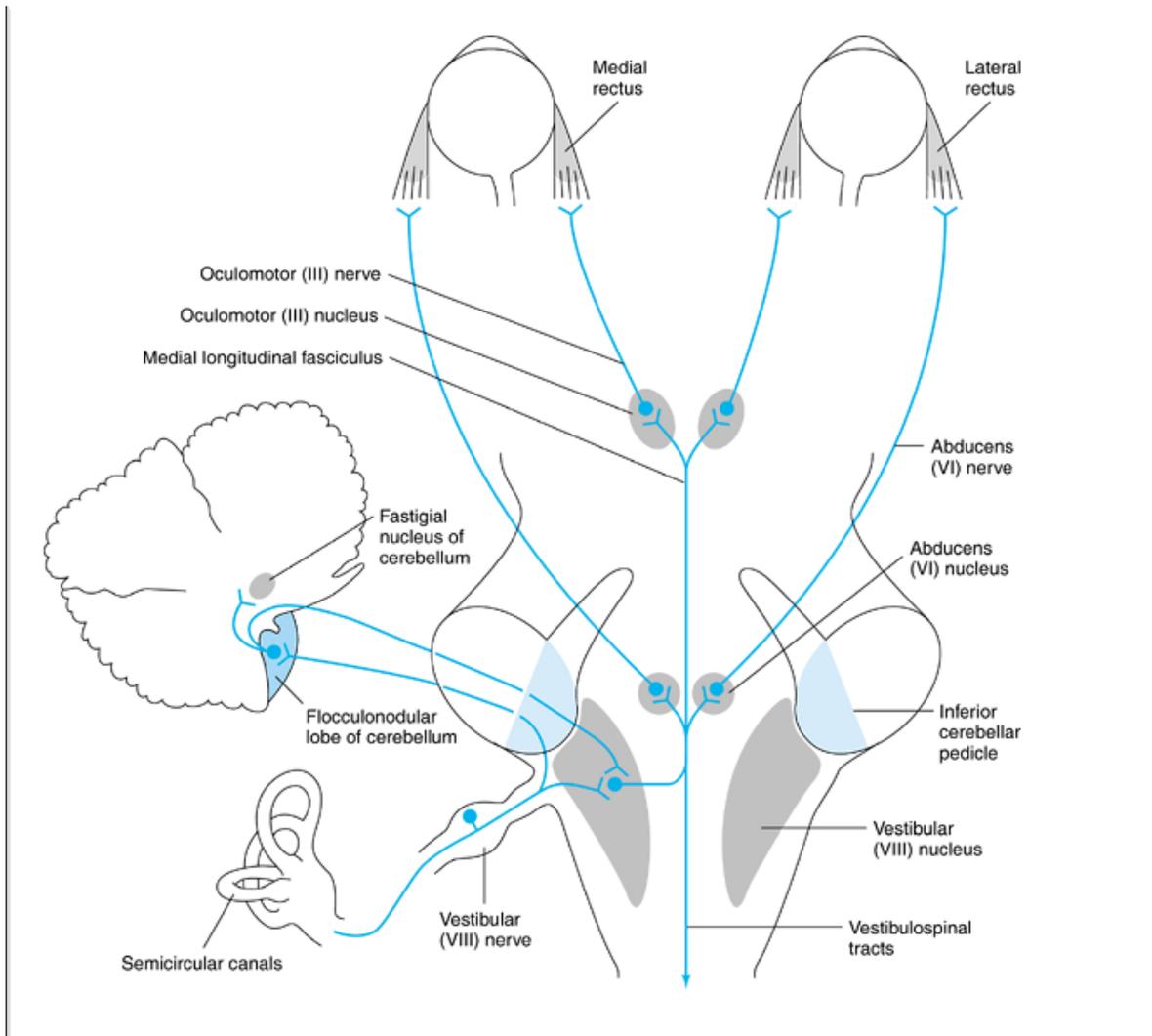
Vertigo must be distinguished from nonvertiginous dizziness, which includes sensations of light-headedness, faintness, or giddiness not associated with an illusion of movement. In contrast to vertigo, these sensations are produced by conditions that impair the brain's supply of blood, oxygen, or glucose—eg, excessive vagal stimulation, orthostatic hypotension, cardiac arrhythmias, myocardial ischemia, hypoxia, or hypoglycemia—and may culminate in loss of consciousness (**syncope**; see Chapter 8).

### Differential Diagnosis

#### A. ANATOMIC ORIGIN

The first step in the differential diagnosis of vertigo is to localize the pathologic process in the peripheral or central vestibular pathways (Figure 3-1.).





**Figure 3-1.** Peripheral and central vestibular pathways. The vestibular nerve terminates in the vestibular nucleus of the brainstem and in midline cerebellar structures that also project to the vestibular nucleus. From here, bilateral pathways in the medial longitudinal fasciculus ascend to the abducens and oculomotor nuclei and descend to the spinal cord.

**Peripheral** vestibular lesions affect the labyrinth of the inner ear or the vestibular division of the acoustic (VIII) nerve. **Central** lesions affect the brainstem vestibular nuclei or their connections. Rarely, vertigo is of cortical origin, occurring as a symptom associated with complex partial seizures.

**B. SYMPTOMS**

Certain characteristics of vertigo, including the presence of any associated abnormalities, can help differentiate between peripheral and central causes (Table 3-1).



	Peripheral	Central
Vertigo	Often intermittent; severe	Often constant; usually less severe
Nystagmus	Always present; unidirectional, never vertical	May be absent; uni- or bidirectional, may be vertical
Associated findings		
Hearing loss or tinnitus	Often present	Rarely present
Intrinsic brain stem signs	Absent	Typically present

**Table 3-1.** Characteristics of central and peripheral vertigo.

1. Peripheral vertigo tends to be intermittent, lasts for briefer periods, and produces more distress than vertigo of central origin. **Nystagmus** (rhythmic oscillation of the eyeballs) is always associated with peripheral vertigo; it is usually unidirectional and never vertical (see below). Peripheral lesions commonly produce additional symptoms of inner ear or acoustic nerve dysfunction, ie, hearing loss and tinnitus.

2. **Central vertigo** may occur with or without nystagmus; if nystagmus is present, it can be vertical, unidirectional, or multidirectional and may differ in character in the two eyes. (Vertical nystagmus is oscillation in a vertical plane; that produced by upgaze or downgaze is not necessarily in the vertical plane.) Central lesions may produce intrinsic brainstem or cerebellar signs, such as motor or sensory deficits, hyperreflexia, extensor plantar responses, dysarthria, or limb ataxia.

## 2. Ataxia

Ataxia is incoordination or clumsiness of movement that is not the result of muscular weakness. It is caused by vestibular, cerebellar, or sensory (proprioceptive) disorders. Ataxia can affect eye movement, speech (producing dysarthria), individual limbs, the trunk, stance, or gait (Table 3-2).

	Vestibular	Cerebellar	Sensory
Vertigo	Present	May be present	Absent
Nystagmus	Present	Often present	Absent
Dysarthria	Absent	May be present	Absent
Limb ataxia	Absent	Usually present (one limb, unilateral, legs only, or all limbs)	Present (typically legs only)
Stance	May be able to stand with feet together; typically worse with eyes closed	Unable to stand with feet together and eyes either open or closed	Often able to stand with feet together and eyes open but not with eyes closed (Romberg's sign)
Vibratory and position sense	Normal	Normal	Impaired
Ankle reflexes	Normal	Normal	Depressed or absent

**Table 3-2.** Characteristics of vestibular, cerebellar, and sensory ataxia.

### Vestibular Ataxia

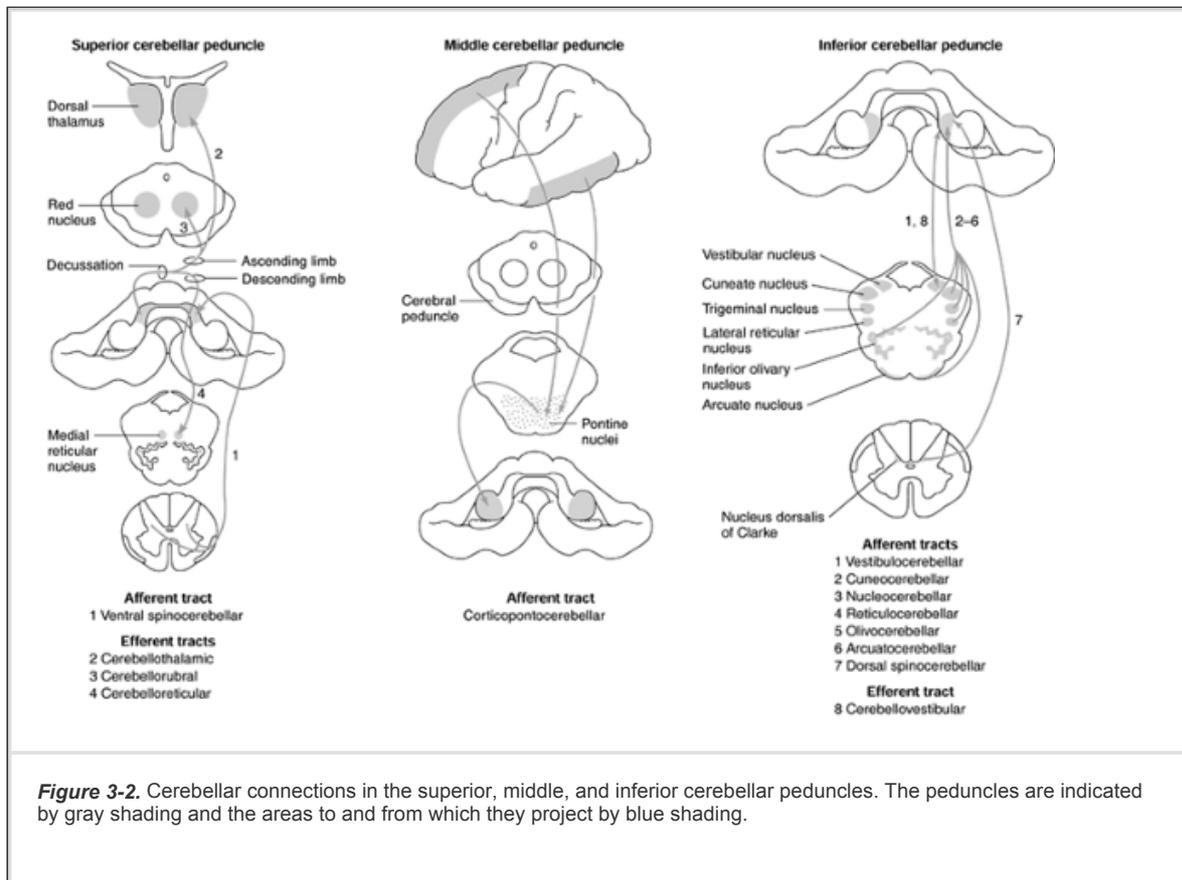
Vestibular ataxia can be produced by the same central and peripheral lesions that cause vertigo. Nystagmus is frequently present and is typically unilateral and most pronounced on gaze away from the side of vestibular involvement. Dysarthria does not occur.

Vestibular ataxia is gravity dependent: Incoordination of limb movements cannot be demonstrated when the

patient is examined lying down but becomes apparent when the patient attempts to stand or walk.

## Cerebellar Ataxia

Cerebellar ataxia is produced by lesions of the cerebellum or its afferent or efferent connections in the cerebellar peduncles, red nucleus, pons, or spinal cord (Figure 3-2). Because of the crossed connection between the frontal cerebral cortex and the cerebellum, unilateral frontal disease can also occasionally mimic a disorder of the contralateral cerebellar hemisphere. The clinical manifestations of cerebellar ataxia consist of irregularities in the rate, rhythm, amplitude, and force of voluntary movements.



### A. HYPOTONIA

Cerebellar ataxia is commonly associated with hypotonia, which results in defective posture maintenance. Limbs are easily displaced by a relatively small force and, when shaken by the examiner, exhibit an increased

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range of excursion. The range of arm swing during walking may be similarly increased. Tendon reflexes take on a pendular quality, so that several oscillations of the limb may occur after the reflex is elicited, although neither the force nor the rate of the reflex is increased. When muscles are contracted against resistance that is then removed, the antagonist muscle fails to check the movement and compensatory muscular relaxation does not ensue promptly. This results in rebound movement of the limb.

### B. INCOORDINATION

In addition to hypotonia, cerebellar ataxia is associated with incoordination of voluntary movements. Simple movements are delayed in onset, and their rates of acceleration and deceleration are decreased. The rate,

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rhythm, amplitude, and force of movements fluctuate, producing a jerky appearance. Because these irregularities are most pronounced during initiation and termination of movement, their most obvious clinical manifestations include **terminal dysmetria**, or "overshoot," when the limb is directed at a target, and **terminal intention tremor** as the limb approaches the target. More complex movements tend to become decomposed into a succession of individual movements rather than a single smooth motor act (**asynergia**). Movements that involve rapid changes in direction or greater physiologic complexity, such as walking, are most severely

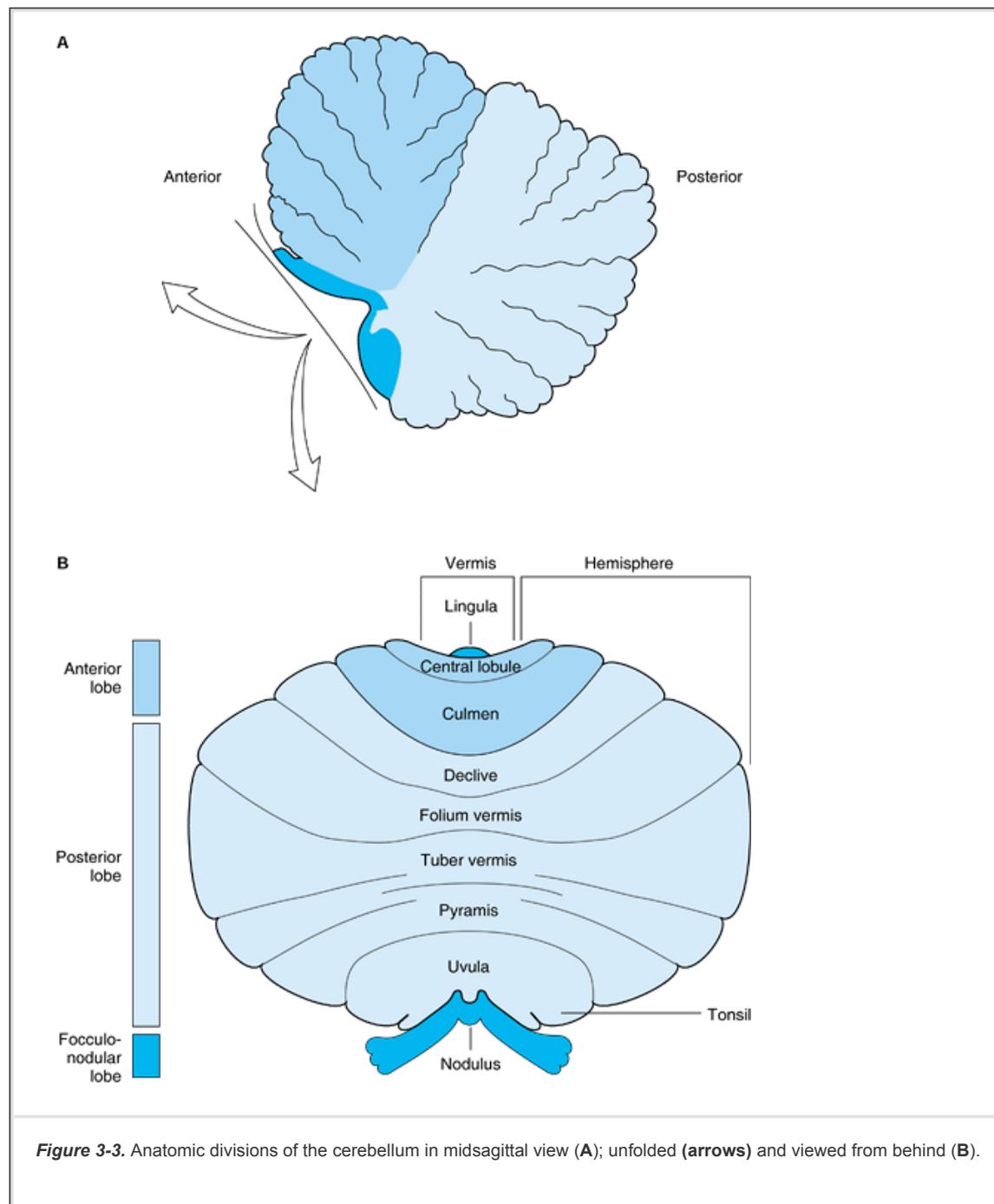
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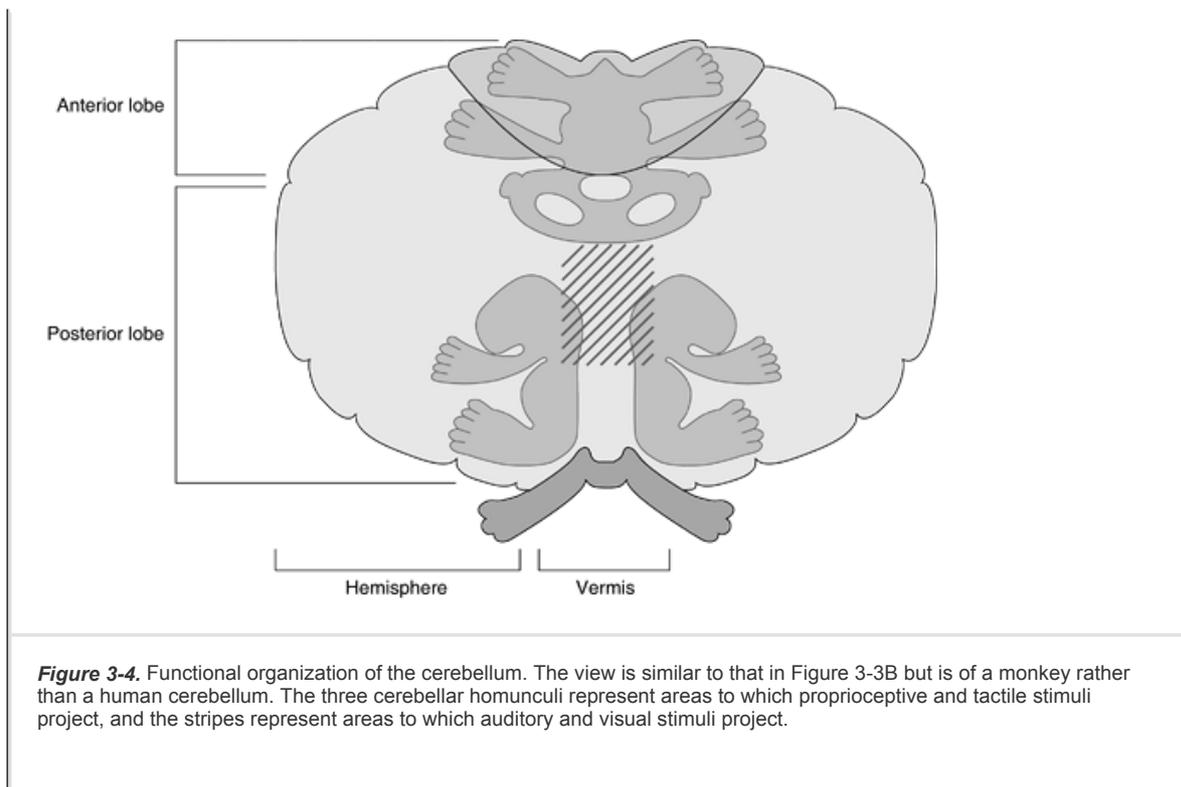
### C. ASSOCIATED OCULAR ABNORMALITIES

Because of the cerebellum's prominent role in the control of eye movements, ocular abnormalities are a frequent consequence of cerebellar disease. These include nystagmus and related ocular oscillations, gaze pareses, and defective saccadic and pursuit movements.

### D. ANATOMIC BASIS OF DISTRIBUTION OF CLINICAL SIGNS

Various anatomic regions of the cerebellum (Figure 3-3) are functionally distinct, corresponding to the somatotopic organization of their motor, sensory, visual, and auditory connections (Figure 3-4).





**Figure 3-4.** Functional organization of the cerebellum. The view is similar to that in Figure 3-3B but is of a monkey rather than a human cerebellum. The three cerebellar homunculi represent areas to which proprioceptive and tactile stimuli project, and the stripes represent areas to which auditory and visual stimuli project.

### 1. Midline lesions

The middle zone of the cerebellum—the vermis and flocculonodular lobe and their associated subcortical (fastigial) nuclei—is involved in the control of axial functions, including eye movements, head and trunk posture, stance, and gait. Midline cerebellar disease therefore results in a clinical syndrome characterized by nystagmus and other disorders of ocular motility, oscillation of the head and trunk (**titubation**), instability of stance, and gait ataxia (Table 3-3). Selective involvement of the superior cerebellar vermis, as commonly occurs in alcoholic cerebellar degeneration, produces exclusively or primarily ataxia of gait, as would be predicted from the somatotopic map of the cerebellum (see Figure 3-4).

Pattern of Involvement	Signs	Causes
Midline	Nystagmus, head and trunk titubation, gait ataxia	Tumor, multiple sclerosis
Superior vermis	Gait ataxia	Wernicke's encephalopathy, alcoholic cerebellar degeneration, tumor, multiple sclerosis
Cerebellar hemisphere	Nystagmus, ipsilateral gaze paresis, dysarthria (especially left hemisphere lesion), ipsilateral hypotonia, ipsilateral limb ataxia, gait ataxia, falling to side of lesion	Infarction, hemorrhage, tumor, multiple sclerosis
Pancerebellar	Nystagmus, bilateral gaze paresis, dysarthria, bilateral hypotonia, bilateral limb ataxia, gait ataxia	Drug intoxications, hypothyroidism, hereditary cerebellar degeneration, paraneoplastic cerebellar degeneration, Wilson's disease, infections and parainfectious encephalomyelitis, Creutzfeldt-Jakob disease, multiple sclerosis

**Table 3-3.** Clinical patterns of cerebellar ataxia.

### 2. Hemispheric lesions

The lateral zones of the cerebellum (cerebellar hemispheres) help to coordinate movements and maintain tone

in the ipsilateral limbs. The hemispheres also have a role in regulating ipsilateral gaze. Disorders affecting one cerebellar hemisphere

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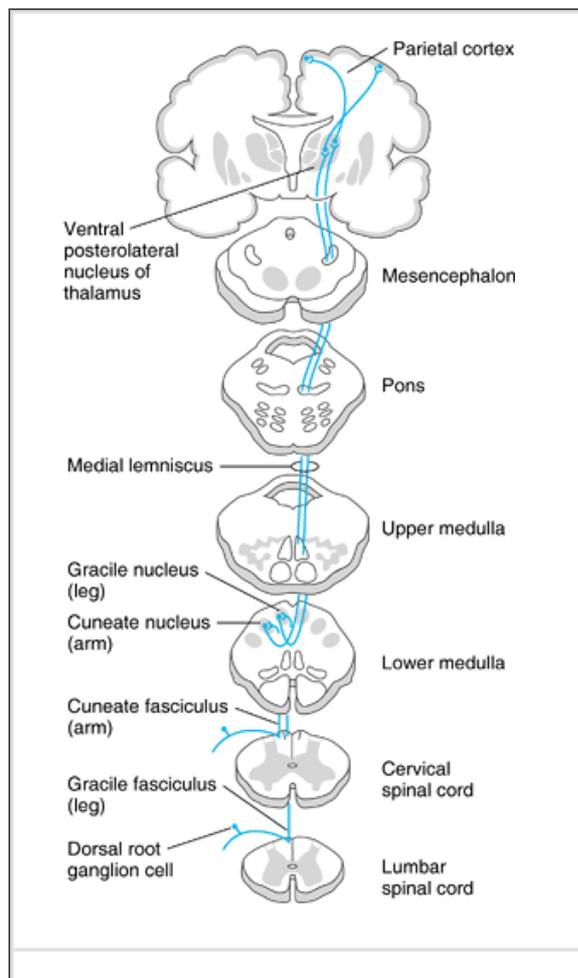
cause ipsilateral hemiataxia and hypotonia of the limbs as well as nystagmus and transient ipsilateral gaze paresis (an inability to look voluntarily toward the affected side). Cerebellar dysarthria may also occur with paramedian lesions in the left cerebellar hemisphere.

### 3. Diffuse disease

Many cerebellar disorders—typically toxic, metabolic, and degenerative conditions—affect the cerebellum diffusely. The clinical picture in such states combines the features of midline and bilateral hemisphere disease.

### Sensory Ataxia

Sensory ataxia results from disorders that affect the proprioceptive pathways in peripheral sensory nerves, sensory roots, posterior columns of the spinal cord, or medial lemnisci. Thalamic and parietal lobe lesions are rare causes of contralateral sensory hemiataxia. Sensations of joint position and movement (**kinesthesia**) originate in pacinian corpuscles and unencapsulated nerve endings in joint capsules, ligaments, muscle, and periosteum. Such sensations are transmitted via heavily myelinated A fibers of primary afferent neurons, which enter the dorsal horn of the spinal cord and ascend uncrossed in the posterior columns (Figure 3-5). Proprioceptive information from the legs is conveyed in the medially located fasciculus gracilis, and information from the arms is conveyed in the more laterally situated fasciculus cuneatus. These tracts synapse on second-order sensory neurons in the nucleus gracilis and nucleus cuneatus in the lower medulla. The second-order neurons decussate as internal arcuate fibers and ascend in the contralateral medial lemniscus. They terminate in the ventral posterolateral nucleus of the thalamus, from which third-order sensory neurons project to the parietal cortex.



**Figure 3-5.** Pathway mediating proprioceptive sensation.

Sensory ataxia from polyneuropathy or posterior column lesions typically affects the gait and legs in symmetric fashion; the arms are involved to a lesser extent or spared entirely. Examination reveals impaired sensations of joint position and movement in the affected limbs, and vibratory sense is also commonly disturbed. Vertigo nystagmus, and dysarthria are characteristically absent.

## **HISTORY**

### **Symptoms & Signs**

#### **A. VERTIGO**

True vertigo must be distinguished from a light-headed or presyncopal sensation. Vertigo is typically described as spinning, rotating, or moving, but when the description is vague, the patient should be asked specifically if the symptom is associated with a sense of movement. The circumstances under which symptoms occur may also be diagnostically helpful. Vertigo is often brought on by changes in head position. The occurrence of symptoms upon arising after prolonged recumbency is a common feature of orthostatic hypotension, and nonvertiginous dizziness related to pancerebral hypoperfusion may be immediately relieved by sitting or lying down. Such hypoperfusion states can lead to loss of consciousness, which is rarely associated with true vertigo. If the problem is identified as vertigo, associated symptoms may help to localize the site of involvement. Complaints of hearing loss or tinnitus strongly suggest a disorder of the peripheral vestibular apparatus (labyrinth or acoustic nerve). Dysarthria, dysphagia, diplopia, or focal weakness or sensory loss affecting the face or limbs indicates the likelihood of a central (brainstem) lesion.

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#### **B. ATAXIA**

Ataxia associated with vertigo suggests a vestibular disorder, whereas numbness or tingling in the legs is common in patients with sensory ataxia. Because proprioceptive deficits may, to some extent, be compensated for by other sensory cues, patients with sensory ataxia may report that their balance is improved by watching their feet when they walk or by using a cane or the arm of a companion for support. They thus find that they are much more unsteady in the dark and may experience particular difficulty in descending stairs.

### **Onset & Time Course**

Establishing the time course of the disorder may suggest its cause. **Sudden** onset of disequilibrium occurs with infarcts and hemorrhages in the brainstem or cerebellum (eg, lateral medullary syndrome, cerebellar hemorrhage or infarction). **Episodic** disequilibrium of acute onset suggests transient ischemic attacks in the basilar artery distribution, benign positional vertigo, or Ménière's disease. Disequilibrium from transient ischemic attacks is usually accompanied by cranial nerve deficits, neurologic signs in the limbs, or both. Ménière's disease is usually associated with progressive hearing loss and tinnitus as well as vertigo.

**Chronic, progressive** disequilibrium evolving over weeks to months is most suggestive of a toxic or nutritional disorder (eg, vitamin B<sub>12</sub> or vitamin E deficiency, nitrous oxide exposure). Evolution over months to years is characteristic of an inherited spinocerebellar degeneration.

### **Medical History**

The medical history should be scrutinized for evidence of diseases that affect the sensory pathways (vitamin B<sub>12</sub> deficiency, syphilis) or cerebellum (hypothyroidism, paraneoplastic syndromes, tumors), and drugs that produce disequilibrium by impairing vestibular or cerebellar function (ethanol, sedative drugs, phenytoin, aminoglycoside antibiotics, quinine, salicylates).

### **Family History**

A hereditary degenerative disorder may be the cause of chronic, progressive cerebellar ataxia. Such disorders include spinocerebellar degenerations, Friedreich's ataxia, ataxia-telangiectasia, and Wilson's disease.

## GENERAL PHYSICAL EXAMINATION

Various features of the general physical examination may provide clues to the underlying disorder.

**Orthostatic hypotension** is associated with certain sensory disorders that produce ataxia—eg, tabes dorsalis, polyneuropathies—and with some cases of spinocerebellar degeneration. The **skin** may show oculocutaneous telangiectasia (ataxia-telangiectasia), or it may be dry, with brittle hair (hypothyroidism) or have a lemon-yellow coloration (vitamin B<sub>12</sub> deficiency). **Pigmented corneal (Kayser-Fleischer) rings** are seen in Wilson's disease (see Chapter 7).

**Skeletal abnormalities** may be present. Kyphoscoliosis is typical in Friedreich's ataxia; hypertrophic or hyperextensible joints are common in tabes dorsalis; and pes cavus is a feature of certain hereditary neuropathies. Abnormalities at the craniocervical junctions may be associated with Arnold-Chiari malformations or other congenital anomalies that involve the posterior fossa.

## NEUROLOGIC EXAMINATION

### Mental Status Examination

An **acute confusional state** with ataxia characterizes ethanol or sedative drug intoxication and Wernicke's encephalopathy.

**Dementia** with cerebellar ataxia is seen in Wilson's disease, Creutzfeldt-Jakob disease, hypothyroidism, paraneoplastic syndromes, and some spinocerebellar degenerations. Dementia with sensory ataxia suggests syphilitic taboparesis or vitamin B<sub>12</sub> deficiency.

**Korsakoff's amnesic syndrome** and cerebellar ataxia are associated with chronic alcoholism.

### Stance & Gait

Observation of stance and gait is helpful in distinguishing between cerebellar, vestibular, and sensory ataxias. In any ataxic patient, the stance and gait are wide-based and unsteady, often associated with reeling or lurching movements.

#### A. STANCE

The ataxic patient asked to stand with the feet together may show great reluctance or an inability to do so. With persistent urging, the patient may gradually move the feet closer together but will leave some space between them. Patients with sensory ataxia and some with vestibular ataxia are, nevertheless, ultimately able to stand with the feet together, compensating for the loss of one source of sensory input (proprioceptive or labyrinthine) with another (visual). This compensation is demonstrated when the patient closes the eyes, eliminating visual cues. With sensory or vestibular disorders, unsteadiness increases and may result in falling (**Romberg's sign**). With a vestibular lesion, the tendency is to fall toward the side of the lesion. Patients with cerebellar ataxia are unable to compensate for their deficit by using visual input and are unstable on their feet whether the eyes are open or closed.

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#### B. GAIT

1. The gait seen in **cerebellar ataxia** is wide-based, often with a staggering quality that might suggest drunkenness. Oscillation of the head or trunk (**titubation**) may be present. If a unilateral cerebellar hemisphere lesion is responsible, there is a tendency to deviate toward the side of the lesion when the patient attempts to walk in a straight line or circle or marches in place with eyes closed. **Tandem** (heel-to-toe) **gait**, which requires walking with an exaggerated narrow base, is always impaired.

2. In **sensory ataxia** the gait is also wide-based and tandem gait is poor. In addition, walking is typically characterized by lifting the feet high off the ground and slapping them down heavily (**steppage gait**) because of impaired proprioception. Stability may be dramatically improved by letting the patient use a cane or lightly rest a hand on the examiner's arm for support. If the patient is made to walk in the dark or with eyes closed, gait is much more impaired.

3. Gait ataxia may also be a manifestation of **conversion disorder** (conversion disorder with motor symptom or deficit) or **malinger**ing. Determining this can be particularly difficult, since isolated gait ataxia without ataxia of individual limbs can also be produced by diseases that affect the superior cerebellar vermis. The most helpful observation in identifying factitious gait ataxia is that such patients often exhibit wildly reeling or

lurching movements from which they are able to recover without falling. In fact, recovery of balance from such awkward positions requires excellent equilibratory function.

### Oculomotor (III), Trochlear (IV), Abducens (VI), & Acoustic (VIII) Nerves

Abnormalities of ocular and vestibular nerve function are typically present with vestibular disease and often present with lesions of the cerebellum. (Examination of cranial nerves III, IV, and VI is discussed in more detail in Chapter 5.)

#### A. OCULAR ALIGNMENT

The eyes are examined in the primary position of gaze (looking directly forward) to detect malalignment in the horizontal or vertical plane.

#### B. NYSTAGMUS AND VOLUNTARY EYE MOVEMENTS

The patient is asked to turn the eyes in each of the cardinal directions of gaze (left, up and left, down and left, right, up and right, down and right; see Chapter 5) to determine whether gaze paresis (impaired ability to move the two eyes coordinately in any of the cardinal directions of gaze) or gaze-evoked nystagmus is present. Nystagmus—an abnormal involuntary oscillation of the eyes—is characterized in terms of the positions of gaze in which it occurs, its amplitude, and the direction of its fast phase. **Pendular nystagmus** has the same velocity in both directions of eye movement; **jerk nystagmus** is characterized by both fast (vestibular-induced) and slow (cortical) phases. The direction of jerk nystagmus is defined by the direction of the fast component. Fast voluntary eye movements (**saccades**) are elicited by having the patient rapidly shift gaze from one target to another placed in a different part of the visual field. Slow voluntary eye movements (**pursuits**) are assessed by having the patient track a slowly moving target such as the examiner's finger.

1. **Peripheral** vestibular disorders produce unidirectional horizontal jerk nystagmus that is maximal on gaze away from the involved side. **Central** vestibular disorders can cause unidirectional or bidirectional horizontal nystagmus, vertical nystagmus, or gaze paresis. **Cerebellar** lesions are associated with a wide range of ocular abnormalities, including gaze pareses, defective saccades or pursuits, nystagmus in any or all directions, and ocular dysmetria (overshoot of visual targets during saccadic eye movements).

2. Pendular nystagmus is usually the result of visual impairment that begins in infancy.

#### C. HEARING

Preliminary examination of the acoustic (VIII) nerve should include otoscopic inspection of the auditory canals and tympanic membranes, assessment of auditory acuity in each ear, and Weber and Rinne tests performed with a 256-Hz tuning fork.

1. In the **Weber test**, unilateral sensorineural hearing loss (from lesions of the cochlea or cochlear nerve) causes the patient to perceive the sound produced by a vibrating tuning fork placed at the vertex of the skull as coming from the normal ear. With a conductive (external or middle ear) disorder, sound is localized to the abnormal ear.

2. The **Rinne test** may also distinguish between sensorineural and conductive defects in the affected ear. Air conduction (tested by holding the vibrating tuning fork next to the external auditory canal) normally produces a louder sound than does bone conduction (tested by placing the base of the tuning fork over the mastoid bone). This pattern also occurs with acoustic nerve lesions but is reversed in the case of conductive hearing loss (Table 3-4).

	Weber Test	Rinne Test
Normal	Sound perceived as coming from midline	Air conduction > bone conduction
Sensorineural hearing loss	Sound perceived as coming from normal ear	Air conduction > bone conduction
Conductive hearing loss	Sound perceived as coming from affected ear	Bone conduction > air conduction on affected side

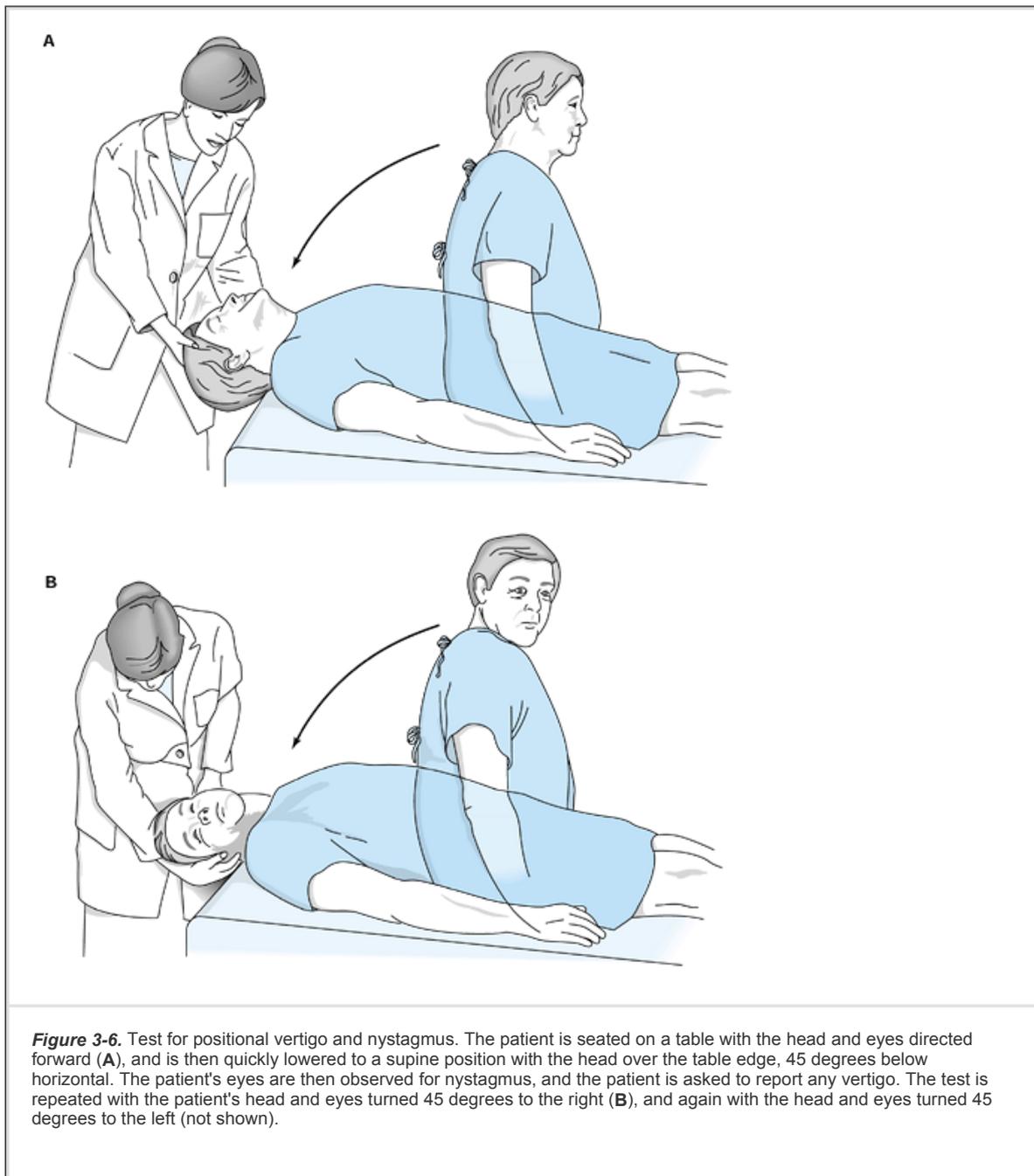
**Table 3-4.** Assessment of hearing loss.

### D. POSITIONAL TESTS

When patients indicate that vertigo occurs with a change in position, the Nylen-Bárány or Dix-Hallpike maneuver (Figure 3-6) is used to try to reproduce the precipitating circumstance. The head, turned to the right, is rapidly lowered 30 degrees below horizontal

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while the gaze is maintained to the right. This process is repeated with the head and eyes turned first to the left and then straight ahead. The eyes are observed for nystagmus, and the patient is asked to note the onset, severity, and cessation of vertigo.



**Positional nystagmus** and **vertigo** are usually associated with peripheral vestibular lesions and are most often a feature of **benign positional vertigo**. This is typically characterized by severe distress, a latency of

several seconds between assumption of the position and the onset of vertigo and nystagmus, a tendency for the response to remit spontaneously (fatigue) as the position is maintained, and attenuation of the response (habituation) as the offending position is repeatedly assumed (Table 3-5). Positional vertigo can also occur with central vestibular disease.

Feature	Peripheral Lesion	Central Lesion
Vertigo	Severe	Mild
Latency	2–40 seconds	No
Fatigability	Yes	No
Habituation	Yes	No

**Table 3-5.** Characteristics of positional nystagmus.

### E. CALORIC TESTING

Disorders of the vestibuloocular pathways can be detected by caloric testing. The patient is placed supine with the head elevated 30 degrees to bring the superficially situated lateral semicircular canal into the upright position. Each ear canal is irrigated in turn with cold (33°C) or warm (44°C) water for 40 seconds, with at least 5 minutes between tests. Warm water tends to produce less discomfort than cold. **Caution:** Caloric testing should be preceded by careful otoscopic examination, and should not be undertaken if the tympanic membrane is perforated.

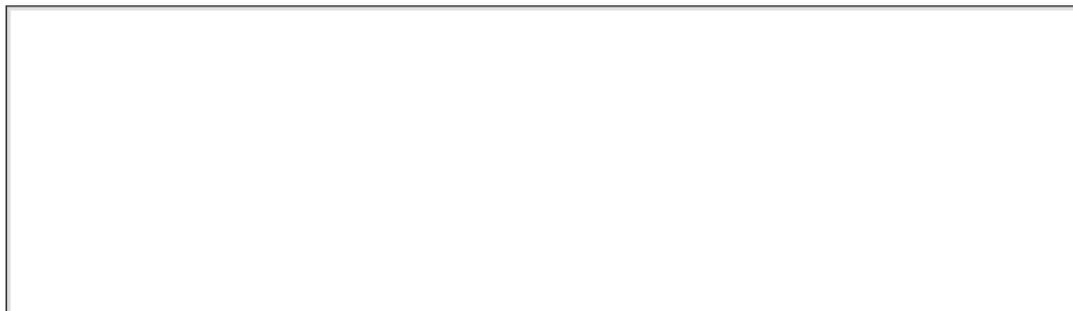
1. In the normal awake patient, cold-water caloric stimulation produces nystagmus with the slow phase toward and the fast phase away from the irrigated ear. Warm water irrigation produces the opposite response.
2. In patients with unilateral labyrinthine, vestibular nerve, or vestibular nuclear dysfunction, irrigation of the affected side fails to cause nystagmus or elicits nystagmus that is later in onset or briefer in duration than on the normal side.

### Other Cranial Nerves

Papilledema associated with disequilibrium suggests an intracranial mass lesion, usually in the posterior fossa, that is causing increased intracranial pressure. Optic neuropathy may be present in multiple sclerosis, neurosyphilis, or vitamin B<sub>12</sub> deficiency. A depressed corneal reflex or facial palsy ipsilateral to the lesion (and the ataxia) can accompany cerebellopontine angle tumor. Weakness of the tongue or palate, hoarseness, or dysphagia results from lower brainstem disease.

### Motor System

Examination of motor function in the patient with a disorder of equilibrium should determine the pattern and severity of ataxia and disclose any associated pyramidal, extrapyramidal, or peripheral nerve involvement that might suggest a cause. The clinical features that help distinguish cerebellar disease from diseases involving these other motor systems are summarized in Table 3-6.



	Cerebellar	Upper Motor Neuron <sup>1</sup>	Lower Motor Neuron <sup>1</sup>	Extrapyramidal <sup>2</sup>
<b>Strength</b>	Normal	Decreased	Decreased	Normal
<b>Tone</b>	Decreased	Increased (spastic) <sup>3</sup>	Normal	Increased (rigid) <sup>3</sup> or decreased
<b>Tendon reflexes</b>	Normal	Increased <sup>3</sup>	Decreased <sup>3</sup>	Normal
<b>Plantar responses</b>	Flexor	Extensor <sup>3</sup>	Flexor	Flexor
<b>Atrophy</b>	Absent	Absent	Present <sup>3</sup> or absent	Absent
<b>Fasciculations</b>	Absent	Absent	Present <sup>3</sup> or absent	Absent
<b>Tremor</b>	Intention tremor <sup>3</sup> or absent	Absent	Absent	Resting tremor <sup>3</sup> or absent
<b>Chorea or athetosis</b>	Absent	Absent	Absent	Present <sup>3</sup> or absent
<b>Akinesia</b>	Absent	Absent	Absent	Present <sup>3</sup> or absent
<b>Ataxia</b>	Present <sup>3</sup>	Absent	Absent	Absent

<sup>1</sup> Also see Chapter 5.

<sup>2</sup> Also see Chapter 7.

<sup>3</sup> Most helpful diagnostic features.

**Table 3-6.** Clinical features distinguishing cerebellar from other motor systems disorders.

## A. ATAXIA AND DISORDERS OF MUSCLE TONE

Muscle tone is assessed as discussed in Chapter 6. Truncal stability is assessed with the patient in the sitting position, and the limbs are examined individually.

1. Movement of the patient's arm is observed as his or her finger tracks back and forth between his or her own nose or chin and the examiner's finger. With mild cerebellar ataxia, an intention tremor characteristically appears near the beginning and end of each such movement, and the patient may overshoot the target.

2. When the patient is asked to raise the arms rapidly to a given height—or when the arms, extended and outstretched in front of the patient, are displaced by a sudden force—there may be overshoot (rebound). Impaired ability to check the force of muscular contractions can also be demonstrated by having the patient forcefully flex the arm at the elbow against resistance—and then suddenly removing the resistance. If the limb is ataxic, continued contraction without resistance may cause the hand to strike the patient at the shoulder or in the face.

3. Ataxia of the legs is demonstrated by the supine patient's inability to run the heel of the foot smoothly up and down the opposite shin.

4. Ataxia of any limb is reflected by irregularity in the rate, rhythm, amplitude, and force of rapid successive tapping movements.

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5. Hypotonia is characteristic of cerebellar disorders; with unilateral cerebellar hemispheric lesions, the ipsilateral limbs are hypotonic.

6. Extrapyramidal hypertonia (rigidity) occurs with cerebellar ataxia in Wilson's disease, acquired hepatocerebral degeneration, Creutzfeldt-Jakob disease,

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and certain types of olivopontocerebellar degeneration.

7. Ataxia with spasticity may be seen in multiple sclerosis, posterior fossa tumors or congenital anomalies, vertebrobasilar ischemia or infarction, olivopontocerebellar degeneration, Friedreich's and other hereditary ataxias, neurosyphilis, Creutzfeldt-Jakob disease, and vitamin B<sub>12</sub> deficiency.

## B. WEAKNESS

The pattern of any weakness should be determined. **Distal neuropathic weakness** can be caused by disorders that produce sensory ataxia, such as polyneuropathies and Friedreich's ataxia. **Paraparesis** may be superimposed on ataxia in vitamin B<sub>12</sub> deficiency, multiple sclerosis, foramen magnum lesions, or spinal cord

tumors. **Ataxic quadriparesis**, **hemiataxia** with **contralateral hemiparesis**, or **ataxic hemiparesis** suggests a brainstem lesion.

### **C. ABNORMAL INVOLUNTARY MOVEMENTS**

**Asterixis** may occur in hepatic encephalopathy, acquired hepatocerebral degeneration, or other metabolic encephalopathies. **Myoclonus** occurs in the same conditions as asterixis and is a prominent manifestation of Creutzfeldt-Jakob disease. **Chorea** may be associated with cerebellar signs in Wilson's disease, acquired hepatocerebral degeneration, or ataxia-telangiectasia.

## **Sensory System**

### **A. JOINT POSITION SENSE**

In patients with sensory ataxia, joint position sense is always impaired in the legs and may be defective in the arms as well. Testing is accomplished by asking the patient to detect passive movement of the joints, beginning distally and moving proximally, to establish the upper level of deficit in each limb. Abnormalities of position sense can also be demonstrated by positioning one limb and having the patient, with eyes closed, place the opposite limb in the same position.

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### **B. VIBRATORY SENSE**

Perception of vibratory sensation is frequently impaired in patients with sensory ataxia. The patient is asked to detect the vibration of a 128-Hz tuning fork placed over a bony prominence. Again, successively more proximal sites are tested to determine the upper level of the deficit in each limb or over the trunk. The patient's threshold for appreciating the vibration is compared with the examiner's own ability to detect it in the hand that holds the tuning fork.

## **Reflexes**

Tendon reflexes are typically hypoactive, with a pendular quality, in cerebellar disorders; unilateral cerebellar lesions produce ipsilateral hyporeflexia. Hyporeflexia of the legs is a prominent manifestation of Friedreich's ataxia, tabes dorsalis, and polyneuropathies that cause sensory ataxia. Hyperactive reflexes and extensor plantar responses may accompany ataxia caused by multiple sclerosis, vitamin B<sub>12</sub> deficiency, focal brainstem lesions, and certain olivopontocerebellar or spinocerebellar degenerations.

## **INVESTIGATIVE STUDIES**

### **Blood Studies**

Blood studies may disclose the hematologic abnormalities associated with vitamin B<sub>12</sub> deficiency, the decreased levels of thyroid hormones in hypothyroidism, the elevated hepatic enzymes and low ceruloplasmin and copper concentrations in Wilson's disease, immunoglobulin deficiency and elevated  $\alpha$ -fetoprotein in ataxia-telangiectasia, antibodies to Purkinje cell antigens in paraneoplastic cerebellar degeneration, or genetic abnormalities associated with hereditary spinocerebellar degenerations.

### **Cerebrospinal Fluid Studies**

The cerebrospinal fluid (CSF) shows elevated protein with cerebellopontine angle tumors (eg, acoustic neuroma), brainstem or spinal cord tumors, hypothyroidism, and some polyneuropathies. Increased protein with pleocytosis is commonly found with infectious or parainfectious encephalitis, paraneoplastic cerebellar degeneration, and neurosyphilis. Although elevated pressure and bloody CSF characterize cerebellar hemorrhage, lumbar puncture is contraindicated if cerebellar hemorrhage is suspected. CSF VDRL is reactive in tabes dorsalis, and oligoclonal immunoglobulin G (IgG) bands may be present in multiple sclerosis or other inflammatory disorders.

### **Imaging**

The **computed tomography (CT) scan** is useful for demonstrating posterior fossa tumors or malformations, cerebellar infarction or hemorrhage, and cerebellar atrophy associated with degenerative disorders. **Magnetic resonance imaging (MRI)** provides better visualization of posterior fossa lesions, including cerebellopontine

angle tumors, and is superior to CT scanning for detecting the lesions of multiple sclerosis.

### **Evoked Potential Testing**

Evoked potential testing, especially of optic pathways (visual evoked potentials), may be helpful in evaluating patients with suspected multiple sclerosis. Brainstem auditory evoked potentials may be abnormal in patients with cerebellopontine angle tumors even though CT scans show no abnormality.

### **Chest X-Ray & Echocardiography**

The chest x-ray or echocardiogram may provide evidence of cardiomyopathy associated with Friedreich's ataxia. The chest x-ray may also show a lung tumor in paraneoplastic cerebellar degeneration.

### **Special Studies**

In vestibular disorders, three additional special investigations may be of help.

#### ***A. AUDIOMETRY***

This is useful when vestibular disorders are associated with auditory impairment; such testing can distinguish conductive, labyrinthine, acoustic nerve, and brainstem disease.

Tests of pure tone hearing are abnormal when sounds are transmitted through air with conductive hearing loss and when transmitted through either air or bone with labyrinthine or acoustic nerve disorders.

Speech discrimination is markedly impaired with acoustic nerve lesions, and is impaired less with disorders of the labyrinth. Speech discrimination is normal in conductive or brainstem involvement.

#### ***B. ELECTRONYSTAGMOGRAPHY (ENG)***

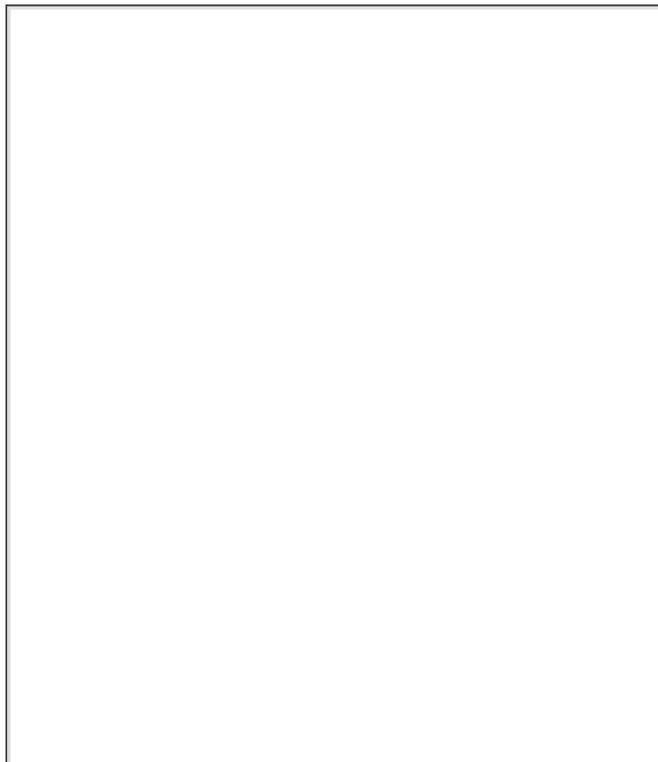
This test can be used to detect and characterize nystagmus, including that elicited by caloric stimulation.

#### ***C. AUDITORY EVOKED RESPONSE***

This test can localize vestibular disease to the peripheral vestibular pathways.

### **PERIPHERAL VESTIBULAR DISORDERS**

A list of peripheral vestibular disorders and features helpful in the differential diagnosis is presented in Table 3-7.



	Hearing Loss		Other Cranial Nerve Palsies
	Conductive	Sensorineural	
Benign positional vertigo	-	-	-
Ménière's disease	-	+	-
Acute peripheral vestibulopathy	-	-	-
Otosclerosis	+	+	-
Head trauma	±	±	±
Cerebellopontine angle tumor	-	+	±
Toxic vestibulopathy			
Alcohol	-	-	-
Aminoglycosides	-	+	-
Salicylates	-	+	-
Quinine	-	+	-
Acoustic (VIII) neuropathy			
Basilar meningitis	-	+	±
Hypothyroidism	-	+	-
Diabetes	-	+	±
Paget's disease of the skull (osteitis deformans)	-	+	±

**Table 3-7.** Differential diagnosis of peripheral vestibular disorders.

## **BENIGN POSITIONAL VERTIGO**

Positional vertigo occurs upon assuming a particular head position. It is usually associated with peripheral vestibular lesions but may also be due to central (brainstem or cerebellar) disease.

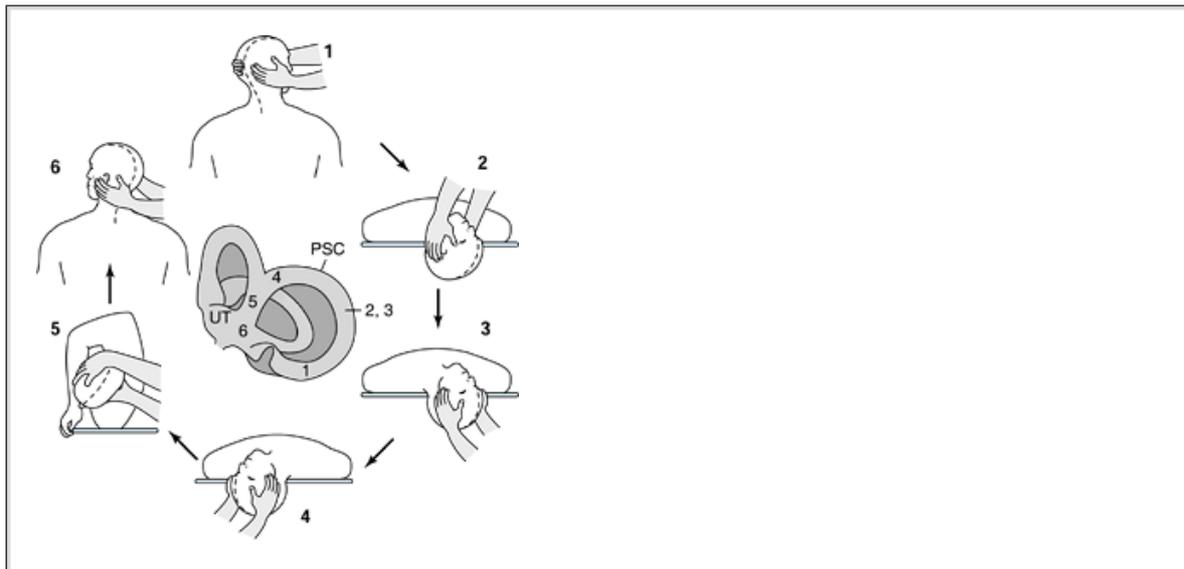
Benign positional vertigo is the most common cause of vertigo of peripheral origin, accounting for about 30% of cases. The most frequently identified cause is head trauma, but in most instances, no cause can be determined. The pathophysiologic basis of benign positional vertigo is thought to be **canalolithiasis**—stimulation of the semicircular canal by debris floating in the endolymph.

The syndrome is characterized by brief (seconds to minutes) episodes of severe vertigo that may be accompanied by nausea and vomiting. Symptoms may occur with any change in head position but are usually most severe in the lateral decubitus position with the affected ear down. Episodic vertigo typically continues for several weeks and then resolves spontaneously; in some cases it is recurrent. Hearing loss is not a feature.

Peripheral and central causes of positional vertigo can usually be distinguished on physical examination by means of the Nysten-Bárány or Dix-Hallpike maneuver (discussed earlier; see Figure 3-6). Positional nystagmus always accompanies vertigo in the benign disorder and is typically unidirectional, rotatory, and delayed in onset by several seconds after assumption of the precipitating head position. If the position is maintained, nystagmus and vertigo resolve within seconds to minutes. If the maneuver is repeated successively, the response is attenuated. In contrast, positional vertigo of central origin tends to be less

severe, and positional nystagmus may be absent. There is no latency, fatigue, or habituation in central positional vertigo.

The mainstay of treatment in most cases of benign positional vertigo of peripheral origin (canalolithiasis) is the use of **repositioning maneuvers** that employ the force of gravity to move endolymphatic debris out of the semicircular canal and into the vestibule, where it can be reabsorbed. In one such maneuver (Figure 3-7), the head is turned 45 degrees in the direction of the affected ear (determined clinically, as described above), and the patient reclines to a supine position, with the head (still turned 45 degrees) hanging down over the end of the examining table. The head, still hanging down, is then turned 90 degrees in the opposite direction, to 45 degrees toward the opposite ear. Next, the patient rolls to a lateral decubitus position with the affected ear up, and the head still turned 45 degrees toward the unaffected ear and hanging down. Finally, the patient turns to a prone position and sits up. Vestibulosuppressant drugs (Table 3-8) may also be useful in the acute period, and vestibular rehabilitation, which promotes compensation for vestibular dysfunction through the recruitment of other sensory modalities, may be helpful as well.



**Figure 3-7.** Repositioning treatment for benign positional vertigo resulting from canalolithiasis. In the example shown, repositioning maneuvers are used to move endolymphatic debris out of the posterior semicircular canal (PSC) of the right ear and into the utricle (UT), the larger of two membranous sacs in the vestibule of the labyrinth, where this debris can be reabsorbed. The numbers (1–6) refer to both the position of the patient and the corresponding location of debris within the labyrinth. The patient is seated and the head is turned 45 degrees to the right (1). The head is lowered rapidly to below the horizontal (2); the examiner shifts position (3); and the head is rotated rapidly 90 degrees in the opposite direction, so it now points 45 degrees to the left, where it remains for 30 seconds (4). The patient then rolls onto the left side without turning the head in relation to the body and maintains this position for another 30 seconds (5) before sitting up (6). This maneuver may need to be repeated until nystagmus is abolished. The patient must then avoid the supine position for at least 2 days. (Courtesy of Baloh, RW. Reproduced with permission from Samuels MA et al: *Office Practice of Neurology*. Churchill Livingstone, 1995.)

Drug	Dosage <sup>2</sup>
<b>Antihistamines</b>	
Meclizine	25 mg PO q4–6h
Promethazine	25–50 mg PO, IM, or PR q4–6h
Dimenhydrinate	50 mg PO or IM q4–6h or 100 mg PR q8h
<b>Anticholinergics</b>	
Scopolamine	0.5 mg transdermally q3d
<b>Benzodiazepines</b>	
Diazepam	5–10 mg PO or IM q4–6h
<b>Sympathomimetics</b>	
Amphetamine	5–10 mg PO q4–6h
Ephedrine	25 mg PO q4–6h

<sup>1</sup> Adapted from Baloh RW, Honrubia V: *Clinical Neurophysiology of the Vestibular System*, 2nd ed. Vol 32 of *Contemporary Neurology Series*. Davis, 1990.

<sup>2</sup> PO, orally; IM, intramuscularly; PR, rectally.

**Table 3-8.** Drugs used in the treatment of vertigo.<sup>1</sup>

## MÉNIÈRE'S DISEASE

Ménière's disease is characterized by repeated episodes of vertigo lasting from minutes to days, accompanied by tinnitus and progressive sensorineural hearing loss. Most cases are sporadic, but familial occurrence has also been described, and may show anticipation, or earlier onset in successive generations. Some cases appear to be related to mutations in the **cochlin** gene on chromosome 14q12–q13. Onset is between the ages of 20 and

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50 years in about three-fourths of cases, and men are affected more often than women. The cause is thought to be an increase in the volume of labyrinthine endolymph (**endolymphatic hydrops**), but the pathogenetic mechanism is unknown.

At the time of the first acute attack, patients may already have noted the insidious onset of tinnitus, hearing loss, and a sensation of fullness in the ear. Acute attacks are characterized by vertigo, nausea, and vomiting and recur at intervals ranging from weeks to years. Hearing deteriorates in a stepwise fashion, with bilateral involvement reported in 10–70% of patients. As hearing loss increases, vertigo tends to become less severe.

Physical examination during an acute episode shows spontaneous horizontal or rotatory nystagmus (or both) that may change direction. Although spontaneous nystagmus is characteristically absent between attacks, caloric testing usually reveals impaired vestibular function. The hearing deficit is not always sufficiently advanced to be detectable at the bedside. Audiometry shows low-frequency pure-tone hearing loss, however, that fluctuates in severity as well as impaired speech discrimination and increased sensitivity to loud sounds.

As has been noted, episodes of vertigo tend to resolve as hearing loss progresses. Treatment is with diuretics, such as hydrochlorothiazide and triamterene. The drugs listed in Table 3-8 may also be helpful during acute attacks. In persistent, disabling, drug-resistant cases, surgical procedures such as endolymphatic shunting, labyrinthectomy, or vestibular nerve section are helpful.

## ACUTE PERIPHERAL VESTIBULOPATHY

This term is used to describe a spontaneous attack of vertigo of inapparent cause that resolves spontaneously and is not accompanied by hearing loss or evidence of central nervous system dysfunction. It includes disorders diagnosed as **acute labyrinthitis** or **vestibular neuronitis**, which are based on unverifiable inferences about the site of disease and the pathogenetic mechanism. A recent antecedent febrile illness can sometimes be identified, however.

The disorder is characterized by vertigo, nausea, and vomiting of acute onset, typically lasting up to 2 weeks. Symptoms may recur, and some degree of vestibular dysfunction may be permanent.

During an attack, the patient—who appears ill—typically lies on one side with the affected ear upward and is

reluctant to move his or her head. Nystagmus with the fast phase away from the affected ear is always present. The vestibular response to caloric testing is defective in one or both ears with about equal frequency. Auditory acuity is normal.

Acute peripheral vestibulopathy must be distinguished from central disorders that produce acute vertigo, such as stroke in the posterior cerebral circulation. Central disease is suggested by vertical nystagmus, altered consciousness, motor or sensory deficit, or dysarthria. Treatment is with a 10- to 14-day course of prednisone, 20 mg orally twice daily, the drugs listed in Table 3-8, or both.

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## **OTOSCLEROSIS**

Otosclerosis is caused by immobility of the stapes, the ear ossicle that transmits vibration of the tympanic membrane to the inner ear. Its most distinctive feature is conductive hearing loss, but sensorineural hearing loss and vertigo are also common; tinnitus is infrequent. Auditory symptoms usually begin before 30 years of age, and familial occurrence is common.

Vestibular dysfunction is most often characterized by recurrent episodic vertigo—with or without positional vertigo—and a sense of positional imbalance. More continuous symptoms may also occur, and the frequency and severity of attacks may increase with time.

Vestibular abnormalities on examination include spontaneous or positional nystagmus of the peripheral type and attenuated caloric responses, which are usually unilateral.

Hearing loss is always demonstrable by audiometry. It is usually of mixed conductive-sensorineural character, and is bilateral in about two-thirds of patients. In patients with episodic vertigo, progressive hearing loss, and tinnitus, otosclerosis must be distinguished from Ménière's disease. Otosclerosis (rather than Ménière's disease) is suggested by a positive family history, a tendency toward onset at an earlier age, the presence of conductive hearing loss, or bilateral symmetric auditory impairment. Imaging studies may also be diagnostically useful.

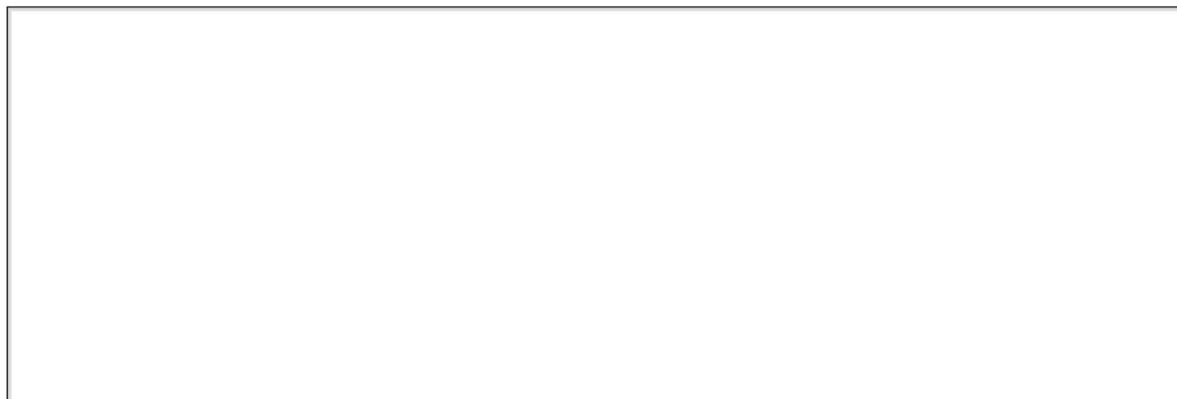
Treatment with a combination of sodium fluoride, calcium gluconate, and vitamin D may be effective. If not, surgical stapedectomy should be considered.

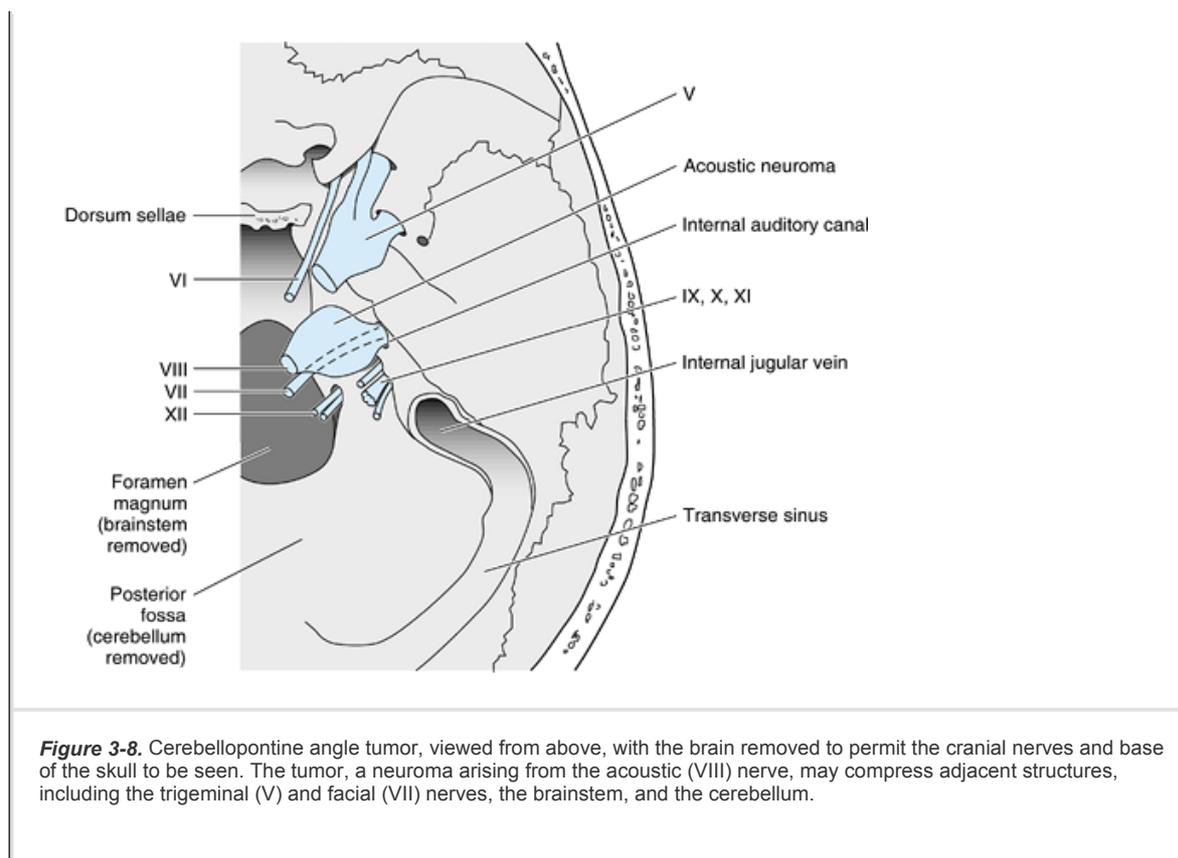
## **HEAD TRAUMA**

Head trauma is the most common identifiable cause of benign positional vertigo. Injury to the labyrinth is usually responsible for posttraumatic vertigo; however, fractures of the petrosal bone may lacerate the acoustic nerve, producing vertigo and hearing loss. Hemotympanum or CSF otorrhea suggests such a fracture.

## **CEREBELLOPONTINE ANGLE TUMOR**

The cerebellopontine angle is a triangular region in the posterior fossa bordered by the cerebellum, the lateral pons, and the petrous ridge (Figure 3-8). By far the most common tumor in this area is the histologically benign **acoustic neuroma** (also termed **neurilemoma**, **neurinoma**, or **schwannoma**), which typically arises from the neurilemmal sheath of the vestibular portion of the acoustic nerve in the internal auditory canal. Less common tumors at this site include **meningiomas** and primary **cholesteatomas** (epidermoid cysts). Symptoms are produced by compression or displacement of the cranial nerves, brainstem, and cerebellum and by obstruction of CSF flow. Because of their anatomic relationship to the acoustic nerve (see Figure 3-8), the trigeminal (V) and facial (VII) nerves are often affected.





Acoustic neuromas occur most often as isolated lesions in patients 30–60 years old, but they may also be a manifestation of neurofibromatosis. **Neurofibromatosis 1 (von Recklinghausen's disease)** is a common autosomal dominant disorder related to mutations in the **neurofibromin** gene on chromosome 17q11.2. In addition to unilateral acoustic neuromas, neurofibromatosis 1 is associated with café-au-lait spots on the skin, cutaneous neurofibromas, axillary or inguinal freckles, optic gliomas, iris hamartomas, and dysplastic bony lesions. **Neurofibromatosis 2** is a rare autosomal dominant disorder caused by mutations in the **neurofibromin 2** gene on chromosome 22q11.1–13.1. Its hallmark is bilateral acoustic neuromas, which may be accompanied by other tumors of the central or peripheral nervous system, including neurofibromas, meningiomas, gliomas, and schwannomas.

## Clinical Findings

### A. SYMPTOMS AND SIGNS

Hearing loss of insidious onset is usually the initial symptom. Less often, patients present with headache, vertigo, gait ataxia, facial pain, tinnitus, a sensation of fullness in the ear, or facial weakness. Although vertigo ultimately develops in 20–30% of patients, a nonspecific

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feeling of unsteadiness is encountered more commonly. In contrast to Ménière's disease, there is a greater tendency for mild vestibular symptoms to persist between attacks. Symptoms may be stable or progress very slowly for months or years.

Unilateral hearing loss of the sensorineural type is the most common finding on physical examination. Other frequently noted abnormalities are ipsilateral facial palsy, depression or loss of the corneal reflex, and sensory loss over the face. Ataxia, spontaneous nystagmus, other lower cranial nerve palsies, and signs of increased intracranial pressure are less common. Unilateral vestibular dysfunction can usually be demonstrated with caloric testing.

### B. LABORATORY FINDINGS

Audiometry shows a sensorineural pattern of deficit with high-frequency pure-tone hearing loss, poor speech discrimination, and marked tone decay. CSF protein is elevated in about 70% of patients, usually in the range of 50–200 mg/dL. The most useful diagnostic radiologic study is MRI of the cerebellopontine angle. Acoustic

neuromas sometimes cause abnormalities of the brainstem auditory evoked potentials at a time when radiologic studies show no abnormalities.

## Differential Diagnosis

Acoustic neuroma must be distinguished from other cerebellopontine angle tumors, the most common being meningioma and cholesteatoma. Meningioma should be considered in patients whose initial symptoms indicate more than isolated acoustic nerve disease. Cholesteatoma is suggested by conductive hearing loss, early facial weakness, or facial twitching, with normal CSF protein. Metastatic carcinoma may also present as a lesion in the cerebellopontine angle.

## Treatment

Treatment is complete surgical excision. In untreated cases, severe complications may result from brainstem compression or hydrocephalus.

## TOXIC VESTIBULOPATHIES

Several drugs can produce vertigo by their effects on the peripheral vestibular system.

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### 1. Alcohol

Alcohol causes an acute syndrome of positional vertigo because of its differential distribution between the cupula and endolymph of the inner ear. Alcohol initially diffuses into the cupula, reducing its density relative to the endolymph. This difference in density makes the peripheral vestibular apparatus unusually sensitive to gravity and thus to position. With time, alcohol also diffuses into the endolymph, and the densities of cupula and endolymph equalize, eliminating the gravitational sensitivity. As the blood alcohol level declines, alcohol leaves the cupula before it leaves the endolymph. This produces a second phase of gravitational sensitivity that persists until the alcohol diffuses out of the endolymph also.

Alcohol-induced positional vertigo typically occurs within 2 hours after ingesting ethanol in amounts sufficient to produce blood levels in excess of 40 mg/dL. It is characterized clinically by vertigo and nystagmus in the lateral recumbent position and is accentuated when the eyes are closed. The syndrome lasts up to about 12 hours and consists of two symptomatic phases separated by an asymptomatic interval of 1–2 hours. Other signs of alcohol intoxication, such as spontaneous nystagmus, dysarthria, and gait ataxia, are caused primarily by cerebellar dysfunction.

### 2. Aminoglycosides

Aminoglycoside antibiotics are widely recognized ototoxins that can produce both vestibular and auditory symptoms. Streptomycin, gentamicin, and tobramycin are the agents most likely to cause vestibular toxicity, and amikacin, kanamycin, and tobramycin are associated with hearing loss. Aminoglycosides concentrate in the perilymph and endolymph and exert their ototoxic effects by destroying sensory hair cells. The risk of toxicity is related to drug dosage, plasma concentration, duration of therapy, conditions—such as renal failure—that impair drug clearance, preexisting vestibular or cochlear dysfunction, and concomitant administration of other ototoxic agents.

Symptoms of vertigo, nausea, vomiting, and gait ataxia may begin acutely; physical findings include spontaneous nystagmus and the presence of Romberg's sign. The acute phase typically lasts for 1 to 2 weeks and is followed by a period of gradual improvement. Prolonged or repeated aminoglycoside therapy may be associated with a chronic syndrome of progressive vestibular dysfunction.

### 3. Salicylates

Salicylates, when used chronically and in high doses, can cause vertigo, tinnitus, and sensorineural hearing loss—all usually reversible when the drug is discontinued. Symptoms result from cochlear and vestibular end-organ damage. Chronic salicylism is characterized by headache, tinnitus, hearing loss, vertigo, nausea, vomiting, thirst, hyperventilation, and sometimes a confusional state. Severe intoxication may be associated with fever, skin rash, hemorrhage, dehydration, seizures, psychosis, or coma. The characteristic laboratory findings are a high plasma salicylate level (about or above 0.35 mg/mL) and combined metabolic acidosis and respiratory alkalosis.

Measures for treating salicylate intoxication include gastric lavage, administration of activated charcoal,

forced diuresis, peritoneal dialysis or hemodialysis, and hemoperfusion.

#### 4. Quinine & Quinidine

Both quinine and quinidine can produce the syndrome of **cinchonism**, which resembles salicylate intoxication in many respects. The principal manifestations are tinnitus, impaired hearing, vertigo, visual deficits (including disorders of color vision), nausea, vomiting, abdominal pain, hot flushed skin, and sweating. Fever, encephalopathy, coma, and death can occur in severe cases. Symptoms result from either overdosage or idiosyncratic reactions (usually mild) to a single small dose of quinine.

#### 5. Cis-Platinum

This antineoplastic drug causes ototoxicity in about 50% of patients. Tinnitus, hearing loss, and vestibular dysfunction are most likely to occur with cumulative doses of 3–4 mg/kg; they may be reversible if the drug is discontinued.

### ACOUSTIC NEUROPATHY

Involvement of the acoustic nerve by systemic disease is an uncommon cause of vertigo. **Basilar meningitis** from bacterial, syphilitic, or tuberculous infection or sarcoidosis can lead to compression of the acoustic and other cranial nerves, but hearing loss is a more common consequence than vertigo. Metabolic disorders associated with acoustic neuropathy include **hypothyroidism**, **diabetes**, and **Paget's disease**.

### CEREBELLAR & CENTRAL VESTIBULAR DISORDERS

Many disorders can produce acute or chronic cerebellar dysfunction (Table 3-9). Several of these conditions may also be associated with central vestibular disorders,

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particularly Wernicke's encephalopathy, vertebrobasilar ischemia or infarction, multiple sclerosis, and posterior fossa tumors.

<p><b>Acute</b></p> <ul style="list-style-type: none"> <li>Drug intoxications: ethanol, sedative-hypnotics, anticonvulsants, hallucinogens</li> <li>Wernicke's encephalopathy<sup>1</sup></li> <li>Vertebrobasilar ischemia or infarction<sup>1</sup></li> <li>Cerebellar hemorrhage</li> <li>Inflammatory disorders</li> </ul> <hr style="border-top: 1px dashed black;"/> <p><b>Chronic</b></p> <ul style="list-style-type: none"> <li>Multiple sclerosis<sup>1,2</sup></li> <li>Alcoholic cerebellar degeneration</li> <li>Phenytoin-induced cerebellar degeneration</li> <li>Hypothyroidism</li> <li>Paraneoplastic cerebellar degeneration</li> <li>Hereditary spinocerebellar ataxias (SCA1–7)</li> <li>Friedreich's ataxia<sup>2</sup></li> <li>Ataxia-telangiectasia</li> <li>Wilson's disease</li> <li>Acquired hepatolenticular degeneration</li> <li>Creutzfeldt-Jakob disease</li> <li>Posterior fossa tumor<sup>1</sup></li> <li>Posterior fossa malformations</li> </ul> <hr style="border-top: 1px solid black;"/> <p><sup>1</sup> May also be associated with central vestibular dysfunction.  <sup>2</sup> May also produce sensory ataxia.</p>
<p><b>Table 3-9.</b> Differential diagnosis of cerebellar ataxia.</p>

### ACUTE DISORDERS

#### 1. Drug Intoxication

Pancerebellar dysfunction manifested by nystagmus, dysarthria, and limb and gait ataxia is a prominent

feature of many drug intoxication syndromes. Agents that produce such syndromes include ethanol, sedative-hypnotics (eg, barbiturates, benzodiazepines, meprobamate, ethchlorvynol, methaqualone), anticonvulsants (such as phenytoin), and hallucinogens (especially phencyclidine). The severity of symptoms is dose related; while therapeutic doses of sedatives or anticonvulsants commonly produce nystagmus, other cerebellar signs imply toxicity.

Drug-induced cerebellar ataxia is often associated with a confusional state, although cognitive function tends to be spared in phenytoin intoxication. The confusional state produced by ethanol and sedative drugs is characterized by somnolence, whereas hallucinogens are more often associated with agitated delirium. In most cases, only general supportive care is necessary. The distinctive features of intoxication with each of these groups of drugs are discussed in detail in Chapter 1.

## 2. Wernicke's Encephalopathy

Wernicke's encephalopathy (see also Chapter 1) is an acute disorder comprising the clinical triad of ataxia, ophthalmoplegia, and confusion. It is caused by thiamine (vitamin B<sub>1</sub>) deficiency and is most common in chronic alcoholics, although it may occur as a consequence of malnutrition from any cause. The major sites of pathologic involvement are the medial thalamic nuclei, mammillary bodies, periaqueductal and periventricular brainstem nuclei (especially those of the oculomotor, abducens, and acoustic nerves), and superior cerebellar vermis. Cerebellar and vestibular involvement both contribute to the ataxia.

Ataxia affects gait primarily or exclusively; the legs themselves are ataxic in only about one-fifth of patients, and the arms in one-tenth. Dysarthria is rare. Other classic findings include an amnesic syndrome or global confusional state, horizontal or combined horizontal-vertical nystagmus, bilateral lateral rectus palsies, and absent ankle jerks. Caloric testing reveals bilateral or unilateral vestibular dysfunction. Conjugate gaze palsies, pupillary abnormalities, and hypothermia can also occur.

The diagnosis is established by the response to administration of thiamine, which is usually given initially in a dose of 100 mg intravenously. Ocular palsies tend to be the earliest deficits to improve and typically begin to do so within hours. Ataxia, nystagmus, and acute confusion start to resolve within a few days. Recovery from ocular palsies is invariably complete, but horizontal nystagmus may persist.

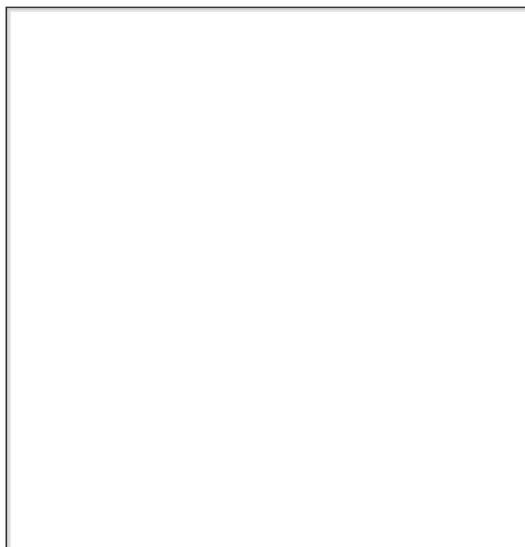
Ataxia is fully reversible in only about 40% of patients; where gait returns fully to normal, recovery typically takes several weeks to months.

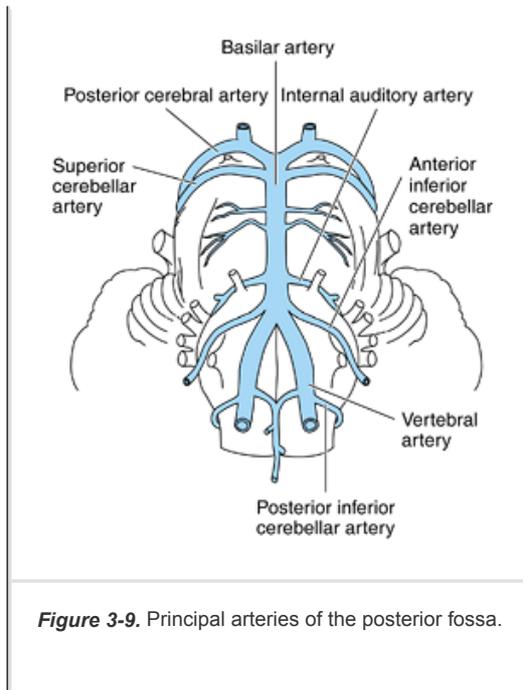
## 3. Vertebrobasilar Ischemia & Infarction

Transient ischemic attacks and strokes in the vertebrobasilar system are often associated with ataxia or vertigo.

### *Internal Auditory Artery Occlusion*

Vertigo of central vestibular origin with unilateral hearing loss results from occlusion of the internal auditory artery (Figure 3-9), which supplies the acoustic nerve. This vessel may originate from the basilar or anterior inferior cerebellar artery. Vertigo is accompanied by nystagmus, with the fast phase directed away from the involved side. Hearing loss is unilateral and sensorineural.

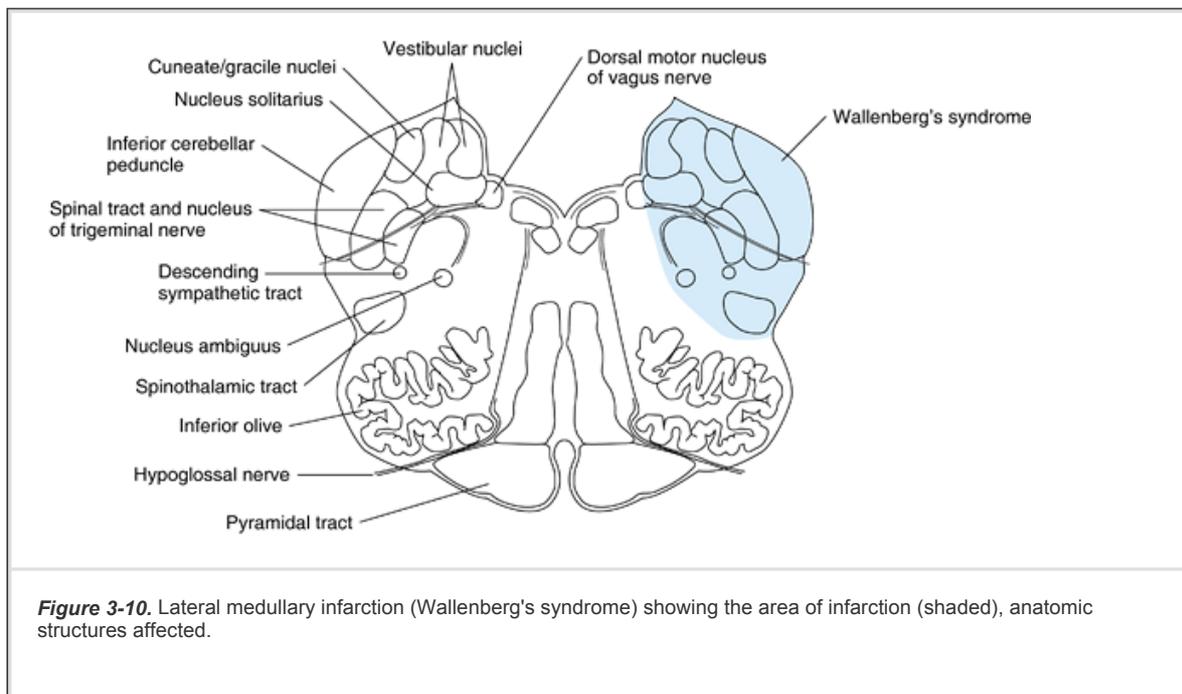




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### Lateral Medullary Infarction

Lateral medullary infarction produces **Wallenberg's syndrome** (Figure 3-10) and is most often caused by proximal vertebral artery occlusion. Clinical manifestations vary, depending on the extent of infarction. They typically consist of vertigo, nausea, vomiting, dysphagia, hoarseness, and nystagmus in addition to ipsilateral Horner's syndrome, limb ataxia, impairment of all sensory modalities over the face, and loss of light touch and position sense in the limbs. There is also impairment of pinprick and temperature appreciation in the contralateral limbs. Vertigo results from involvement of the vestibular nuclei and hemiataxia from involvement of the inferior cerebellar peduncle.

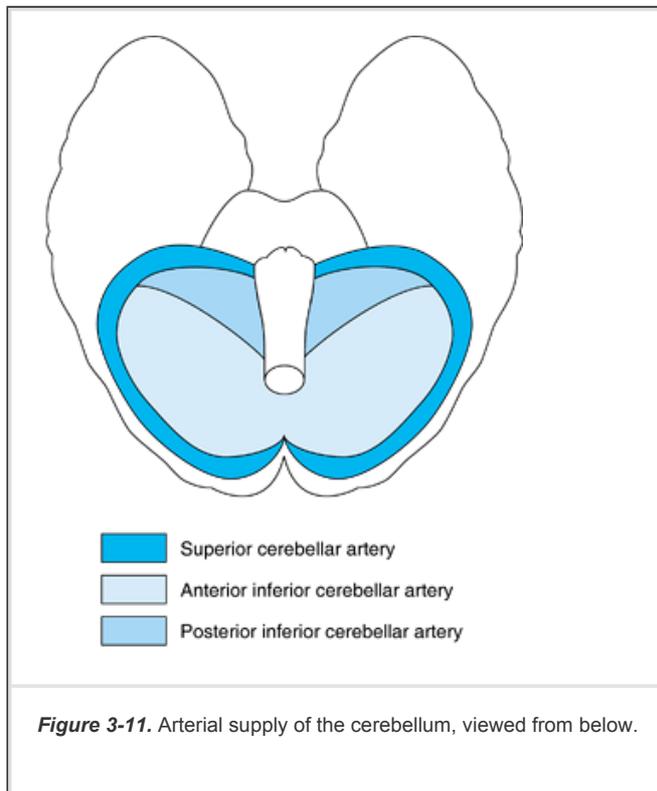


### Cerebellar Infarction

The cerebellum is supplied by three arteries: the superior cerebellar, anterior inferior cerebellar, and posterior inferior cerebellar. The territory supplied by each of these vessels is highly variable, both from one individual

to another and between the two sides of the cerebellum in a given patient. The superior, middle, and inferior cerebellar peduncles are typically supplied by the superior, anterior inferior, and posterior inferior cerebellar arteries, respectively.

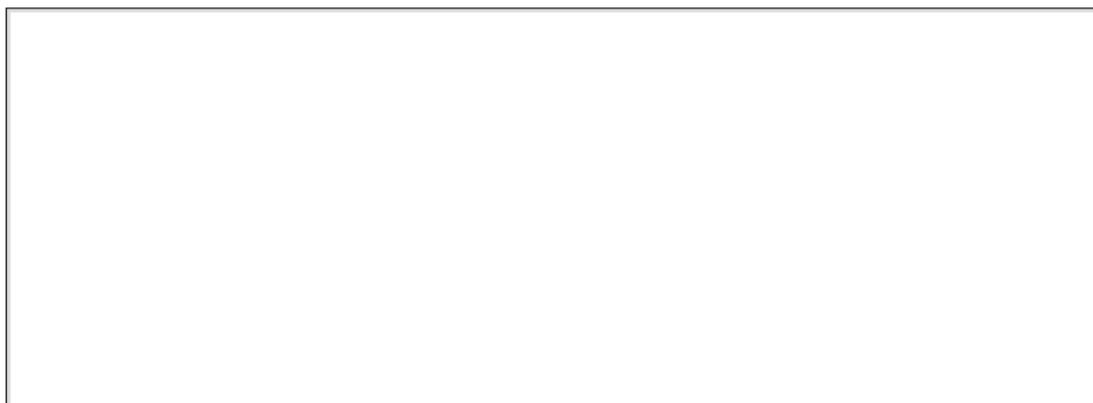
Cerebellar infarction results from occlusion of a cerebellar artery (Figure 3-11); the clinical syndromes produced can be distinguished only by the associated brainstem findings. In each case, cerebellar signs include ipsilateral limb ataxia and hypotonia. Other symptoms and signs such as headache, nausea, vomiting, vertigo, nystagmus, dysarthria, ocular or gaze palsies, facial weakness or sensory loss, and contralateral hemiparesis or hemisensory deficit may be present. Brainstem infarction or compression by cerebellar edema can result in coma and death.

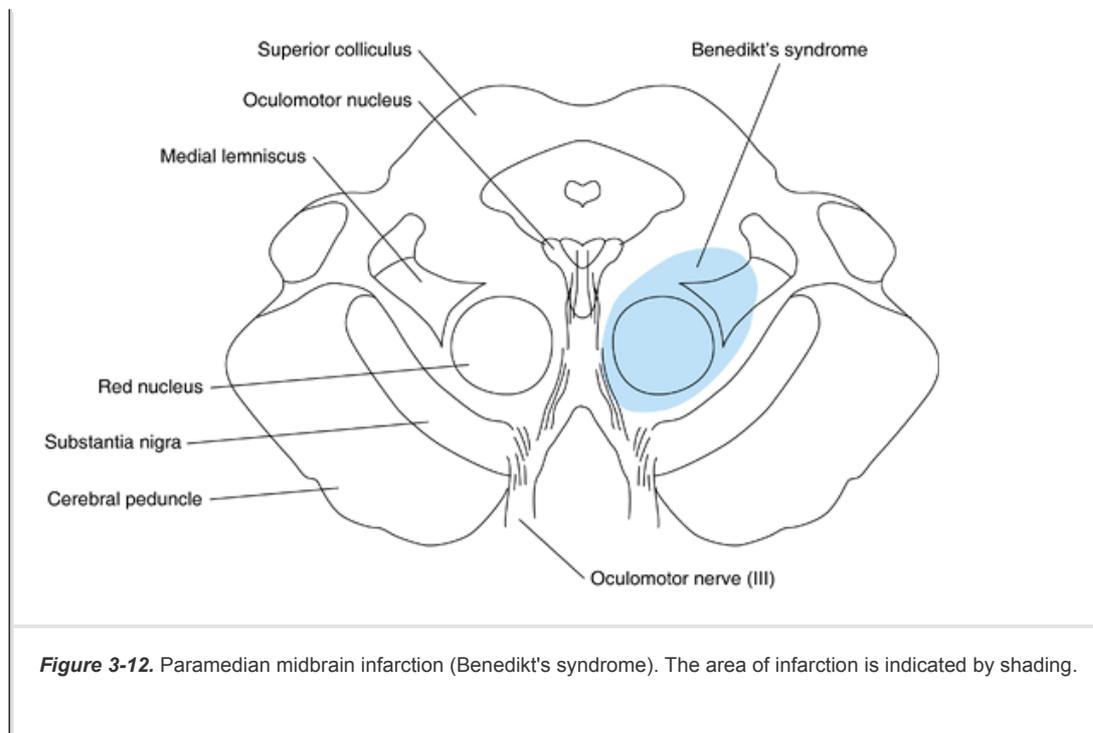


**3** The diagnosis of cerebellar infarction is made by CT scan or MRI, which allows differentiation between infarction and hemorrhage; it should be obtained promptly. When brainstem compression occurs, surgical decompression and resection of infarcted tissue can be lifesaving.

### ***Paramedian Midbrain Infarction***

Paramedian midbrain infarction caused by occlusion of the paramedian penetrating branches of the basilar artery affects the third nerve root fibers and red nucleus (Figure 3-12). The resulting clinical picture (**Benedikt's syndrome**) consists of ipsilateral medial rectus palsy with a fixed dilated pupil and contralateral limb ataxia (typically affecting only the arm). Cerebellar signs result from involvement of the red nucleus, which receives a crossed projection from the cerebellum in the ascending limb of the superior cerebellar peduncle.





#### 4. Cerebellar Hemorrhage

Most cerebellar hemorrhages are due to hypertensive vascular disease; less common causes include anticoagulation, arteriovenous malformation, blood dyscrasia, tumor, and trauma. Hypertensive cerebellar hemorrhages are usually located in the deep white matter of the cerebellum and commonly extend into the fourth ventricle.

The classic clinical picture of hypertensive cerebellar hemorrhage consists of the sudden onset of headache, which may be accompanied by nausea, vomiting, and vertigo, followed by gait ataxia and impaired consciousness, usually evolving over a period of hours. At the time of presentation, patients can be fully alert, confused, or comatose. In alert patients, nausea and vomiting are often prominent. The blood pressure is typically elevated, and nuchal rigidity may be present. The pupils are often small and sluggishly reactive. Ipsilateral gaze palsy (with gaze preference away from the side of hemorrhage) and ipsilateral peripheral facial palsy are common. The gaze preference cannot be overcome by caloric stimulation. Nystagmus and ipsilateral depression of the corneal reflex may occur. The patient, if alert, exhibits ataxia of stance and gait; limb ataxia is less common. In the late stage of brainstem compression, the legs are spastic and extensor plantar responses are present.

The CSF is frequently bloody, but lumbar puncture should be avoided if cerebellar hemorrhage is suspected, because it may lead to a herniation syndrome.

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**3** The diagnostic procedure of choice is a CT scan. Treatment consists of surgical evacuation of the hematoma, a procedure that can be lifesaving.

#### 5. Inflammatory Disorders

Acute inflammatory disorders of the cerebellum mediated by infection or immune mechanisms are important and often reversible causes of ataxia. Cerebellar ataxia caused by **viral infection** is one of the principal manifestations of St. Louis encephalitis. AIDS dementia complex and meningoencephalitis associated with varicella, mumps, poliomyelitis, infectious mononucleosis, and lymphocytic choriomeningitis can also produce cerebellar symptoms. **Bacterial infection** is a less common cause of cerebellar ataxia; 10–20% of brain abscesses are located in the cerebellum, however, and ataxia may be a feature of *Haemophilus influenzae* meningitis in children. A cerebellar syndrome has been described in legionnaires' disease, usually without clinical evidence of meningitis.

Several conditions that may occur following an acute febrile illness or vaccination produce cerebellar ataxia that is assumed to be of autoimmune origin.

### **Acute Cerebellar Ataxia of Childhood**

Acute cerebellar ataxia of childhood is a syndrome characterized by severe gait ataxia that usually resolves completely

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within months. It generally follows an acute viral infection or inoculation. A full discussion of cerebellar ataxia in childhood is beyond the scope of this chapter.

### **Acute Disseminated Encephalomyelitis**

This immune-mediated disorder may cause demyelination and inflammatory changes in the cerebellar white matter, producing ataxia that is often associated with impaired consciousness, seizures, focal neurological signs, or myelopathy.

### **Fisher Variant of Guillain-Barré Syndrome**

Cerebellar ataxia, external ophthalmoplegia, and areflexia constitute this variant of Guillain-Barré syndrome. Symptoms develop over a few days. Ataxia primarily affects the gait and trunk, with lesser involvement of the individual limbs; dysarthria is uncommon. CSF protein may be elevated. Respiratory insufficiency occurs rarely, and the usual course is of gradual and often complete recovery over weeks to months. The ataxia is similar to that of cerebellar disease, but it is not yet known whether it arises centrally or peripherally.

## **CHRONIC DISORDERS**

### **1. Multiple Sclerosis**

Multiple sclerosis can produce disorders of equilibrium of cerebellar, vestibular, or sensory origin. Cerebellar signs are associated with demyelinated areas (plaques) in the white matter of the cerebellum, cerebellar peduncles, or brainstem. As is the case with other manifestations of multiple sclerosis, these signs may remit and relapse.

Involvement of vestibular pathways in the brainstem produces vertigo, which may be acute in onset and sometimes positional. Vertigo, which is rarely the first symptom of multiple sclerosis, is not uncommon during the course of the disease.

Gait ataxia from cerebellar involvement is a presenting complaint in 10–15% of patients. Cerebellar signs are present in about one-third of patients on initial examination; they ultimately develop in twice that number.

Nystagmus is one of the most common physical findings; it can occur with or without other evidence of cerebellar dysfunction. Dysarthria also occurs frequently. When gait ataxia occurs, it is most often cerebellar rather than sensory in origin. Ataxia of the limbs is common; it is usually bilateral and tends to affect either both legs or all four limbs.

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Evidence that a cerebellar disorder is due to multiple sclerosis may be found in a history of remitting and relapsing neurologic dysfunction that affects multiple sites in the central nervous system; from such associated abnormalities as optic neuritis, internuclear ophthalmoplegia, or pyramidal signs; or from laboratory investigations. CSF analysis may reveal oligoclonal bands, elevated IgG, increased protein, or a mild lymphocytic pleocytosis. Visual, auditory, or somatosensory evoked response recording can document subclinical sites of involvement. The CT scan or MRI may show areas of demyelination. It must be emphasized, however, that no laboratory finding is itself diagnostic of multiple sclerosis, and the history and neurologic examination must be primarily relied upon in arriving at such a diagnosis.

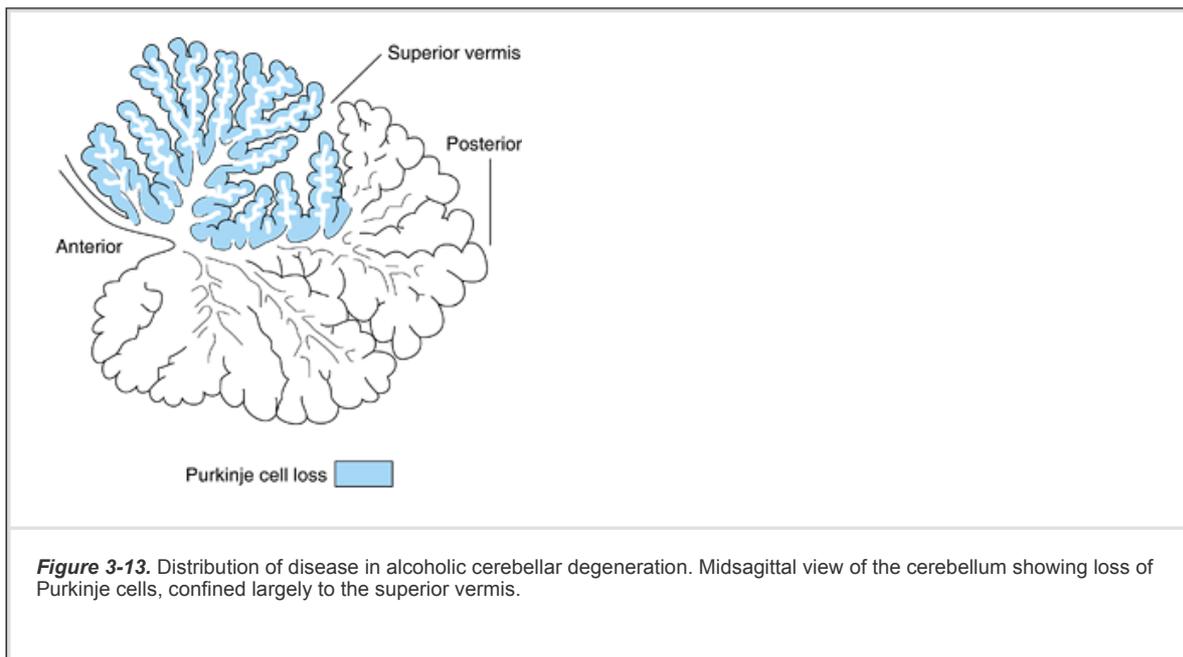
Multiple sclerosis is discussed in more detail in Chapter 5.

### **2. Alcoholic Cerebellar Degeneration**

A characteristic cerebellar syndrome may develop in chronic alcoholics, probably as a result of nutritional deficiency. Affected patients typically have a history of daily or binge drinking lasting 10 or more years with associated dietary inadequacy. Most have experienced other medical complications of alcoholism: liver disease, delirium tremens, Wernicke's encephalopathy, or polyneuropathy. Alcoholic cerebellar degeneration is most common in men and usually has its onset between the ages of 40 and 60 years.

Degenerative changes in the cerebellum are largely restricted to the superior vermis (Figure 3-13); because

this is also the site of cerebellar involvement in Wernicke's encephalopathy, both disorders may be part of the same clinical spectrum.



Alcoholic cerebellar degeneration is usually insidious in onset; it is gradually progressive, eventually reaching a stable level of deficit. Progression over weeks to months is more common than is deterioration over years; in occasional cases, ataxia appears abruptly or is mild and stable from the onset.

Gait ataxia is a universal feature and is almost always the problem that initially commands medical attention. The legs are also ataxic on heel-knee-shin testing in about 80% of patients. Commonly associated findings are distal sensory deficits in the feet and absent ankle reflexes—from polyneuropathy—and signs of malnutrition such as loss of subcutaneous tissue, generalized muscle atrophy, or glossitis. Less frequent manifestations include ataxia of the arms, nystagmus, dysarthria, hypotonia, and truncal instability.

CT scan or MRI may show cerebellar atrophy (Figure 3-14), but this is a nonspecific finding that can be encountered in any degenerative disorder that affects the cerebellum.



**Figure 3-14.** CT scan in alcoholic cerebellar degeneration, showing marked atrophy of the cerebellar vermis with relative

sparing of the cerebellar hemispheres. (Courtesy of A Gean.)

Chronic cerebellar ataxia that begins in adulthood and primarily affects gait can also occur in hypothyroidism, paraneoplastic syndromes, idiopathic cerebellar degenerations, and anomalies at the craniocervical junction such as Arnold-Chiari malformation. The possibility of hypothyroidism or systemic cancer, which may be treatable, should be investigated with thyroid function tests, chest x-ray, and, in women, breast and pelvic examinations.

No specific treatment is available for alcoholic cerebellar degeneration. Nonetheless, all patients with this diagnosis should receive thiamine because of the apparent role of thiamine deficiency in the pathogenesis of Wernicke's encephalopathy, a closely related syndrome. Abstinence from alcohol, combined with adequate nutrition, leads to stabilization in most cases.

### 3. Phenytoin-Induced Cerebellar Degeneration

Chronic therapy with phenytoin, often with drug levels in the toxic range, may cause cerebellar degeneration that affects the cerebellar hemispheres and inferior and posterior vermis most severely, while the superior vermis is relatively spared. Clinical features include nystagmus, dysarthria, and ataxia affecting the limbs, trunk, and gait. Polyneuropathy may be present. Symptoms are typically irreversible, but tend to stabilize when the drug is discontinued.

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### 4. Hypothyroidism

Among the neurologic disorders associated with hypothyroidism is a subacute or chronically progressive cerebellar syndrome. This condition may complicate hypothyroidism (of various causes) and is most common in middle-aged or elderly women. Symptoms evolve over a period of months to years. Systemic symptoms of myxedema usually precede the appearance of the cerebellar disorder, but patients occasionally present first with ataxia.

Gait ataxia is the most prominent finding and is present in all patients; ataxia of the limbs, which is also common, may be asymmetric. Dysarthria and nystagmus occur less frequently. Patients may exhibit other neurologic disorders related to hypothyroidism, including sensorineural hearing loss, carpal tunnel syndrome, neuropathy, or myopathy.

Laboratory studies show decreased blood levels of thyroid hormones, elevated thyroid-stimulating hormone (TSH), and often increased CSF protein.

Replacement therapy with levothyroxine, 25–50 µg, increased gradually to 100–200 µg/d orally, usually produces definite but incomplete improvement.

### 5. Paraneoplastic Cerebellar Degeneration

Cerebellar degeneration can also occur as a remote effect of systemic cancer. Lung cancer (especially small-cell), ovarian cancer, Hodgkin's disease, and breast cancer are the most commonly associated neoplasms.

Paraneoplastic degeneration affects the cerebellar vermis and hemispheres diffusely. The pathogenetic mechanism in many cases appears to involve antibodies to tumor cell antigens that cross-react with cerebellar Purkinje cells. Cerebellar symptoms may appear before or after the diagnosis of systemic cancer and typically develop over months. Although the disorder usually progresses steadily, it may stabilize; remission has been described with treatment of the underlying neoplasm.

Gait and limb ataxia are characteristically prominent, and dysarthria occurs in most cases. The limbs may be affected asymmetrically. Nystagmus is rare. Paraneoplastic involvement of other regions of the nervous system may produce associated dysphagia, dementia, memory disturbance, pyramidal signs, or neuropathy. Anti-Purkinje cell antibodies, such as anti-Yo (ovarian and breast cancer), or antinuclear antibodies, such as anti-Hu (small-cell lung cancer) and anti-Ri (breast cancer), can sometimes be detected in the blood (Table 3-10). The CSF may show a mild lymphocytic pleocytosis or elevated protein.

Syndrome	Antigen					
	<i>Hu</i>	<i>Yo</i>	<i>Ri</i>	<i>Ma</i>	<i>Ta</i>	$\alpha_{1A}$ <sup>1</sup>
Cerebellar degeneration	+	+	+	+	+	
Limbic encephalitis	+		+	+		
Sensory neuronopathy	+					
Opsoclonus/myoclonus	+	+	+			
Lambert-Eaton syndrome						+

<sup>1</sup> P/Q-type voltage-gated calcium channel,  $\alpha_{1A}$ -subunit.

**Table 3-10.** Antineuronal autoantibodies in paraneoplastic syndromes.

The diagnosis of paraneoplastic cerebellar degeneration is most difficult when the neurologic symptoms precede the discovery of underlying cancer. The frequent occurrence of dysarthria and dysphagia helps to distinguish this condition from the cerebellar syndromes produced by chronic alcoholism or hypothyroidism. Ataxia of the arms also suggests that alcohol is an unlikely cause. Wernicke's encephalopathy should always be considered because of the susceptibility of patients with cancer to malnutrition.

## 6. Autosomal Dominant Spinocerebellar Ataxias

The hereditary spinocerebellar degenerations (Table 3-11) are a group of inherited disorders characterized by slowly progressive cerebellar ataxia that affects gait early and severely and may eventually confine the patient to bed. These disorders show considerable clinical variability, even within a given family. Most autosomal dominant forms, termed **spinocerebellar ataxias** or **SCAs**, begin in adulthood and show **anticipation**, in which the age at onset decreases, the disease severity increases, or both, in successive generations.

Disease	Gene	Protein	Gene Defect	Syndrome
<b>Autosomal recessive</b>				
FA <sup>1</sup>	<i>FRDA1</i>	Frataxin	GAA <sub>n</sub> <sup>2</sup>	<sup>3</sup>
<b>Autosomal dominant</b>				
SCA1 <sup>4</sup>	<i>SCA1</i>	Ataxin-1	CAG <sub>n</sub>	ADCA I <sup>5</sup>
SCA 2	<i>SCA2</i>	Ataxin-2	CAG <sub>n</sub>	ADCA I
SCA 3/MJD <sup>6</sup>	<i>SCA3</i>	Ataxin-3	CAG <sub>n</sub>	ADCA I
SCA 4	<i>SCA4</i>	Unknown	Unknown	ADCA I
SCA 5	<i>SCA5</i>	Unknown	Unknown	ADCA III
SCA 6	<i>CACNL1A4</i>	Ca channel <sup>7</sup>	CAG <sub>n</sub>	ADCA III
SCA 7	<i>SCA7</i>	Ataxin-7	CAG <sub>n</sub>	ADCA II
SCA 8	<i>SCA8</i>	Unknown	CTG <sub>n</sub>	ADCA I
SCA 10	<i>SCA10</i>	Ataxin-10	ATTCT <sub>n</sub>	ADCA III
SCA 11	<i>SCA11</i>	Unknown	Unknown	ADCA III
SCA 12	<i>PPP2R2B</i>	PPase2 <sup>8</sup>	CAG <sub>n</sub>	ADCA I
SCA 13	<i>SCA13</i>	Unknown	Unknown	<sup>9</sup>
SCA 14	<i>SCA14</i>	Unknown	Unknown	ADCA III
SCA 15	<i>SCA15</i>	Unknown	Unknown	ADCA III
SCA 16	<i>SCA16</i>	Unknown	Unknown	ADCA III
SCA17	<i>TBP</i>	TATA-binding protein	CAG <sub>n</sub>	ADCA I

<sup>1</sup> FA, Friedreich's ataxia.

<sup>2</sup> XYZ<sub>n</sub>, expanded XYZ trinucleotide repeat; VWXYZ<sub>n</sub>, expanded VWXYZ pentanucleotide repeat.

<sup>3</sup> Childhood onset, ataxia, dysarthria, pyramidal signs, neuropathy, scoliosis, cardiomyopathy, diabetes.

<sup>4</sup> SCA, spinocerebellar ataxia.

<sup>5</sup> ADCA I includes ataxia, dysarthria, pyramidal signs, extrapyramidal signs, ophthalmoplegia and dementia; ADCA II includes ataxia, dysarthria, and pigmentary maculopathy; ADCA III includes ataxia, dysarthria, and sometimes mild pyramidal signs.

<sup>6</sup> MJD, Machado-Joseph disease (same as SCA3).

<sup>7</sup> P/Q-type voltage-gated calcium channel,  $\alpha_{1A}$ -subunit.

<sup>8</sup> Protein phosphatase 2, regulatory subunit B,  $\beta$  isoform.

<sup>9</sup> Childhood onset, ataxia, and mental retardation.

**Table 3-11.** Genetic and clinical features of hereditary spinocerebellar ataxias.

Autosomal dominant spinocerebellar ataxia is genetically heterogeneous. The best characterized gene defects are expanded CAG trinucleotide repeats coding for

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polyglutamine tracts in proteins without known function (**ataxins**), and in the  $\alpha_{1A}$ -subunit of the P/Q-type calcium channel, which is found on nerve terminals. Other types of mutations include expanded CTG trinucleotide (SCA8) and ATTCT pentanucleotide (SCA10) repeats. In many cases, the size of these expansions correlates with disease severity and inversely with age at onset.

The gain-of-function mutations seen in SCAs appear to alter the properties of the mutated protein, which cannot be processed normally. The abnormally processed fragments are conjugated with **ubiquitin**, a protein involved in nonlysosomal degradation of defective proteins, with which they are transported to the nucleus in a complex called a **proteasome**. The precise relationship of this accumulation to the neurotoxicity that results from these mutations is uncertain, but intranuclear protein aggregates may interfere with nuclear function.

Atrophy of the cerebellum and sometimes also of the brainstem may be apparent on CT or MRI scans (Figure 3-15). However, definitive diagnosis is by demonstrating one of the known SCA gene defects on genetic testing. There is no specific treatment for the spinocerebellar ataxias, but occupational and physical therapy and devices to assist ambulation may be helpful, and genetic counseling may be indicated.



**Figure 3-15.** CT scan in spinocerebellar atrophy, showing an atrophic cerebellum and brainstem. (Courtesy of A Gean.)

## 7. Friedreich's Ataxia

Among the idiopathic degenerative disorders that produce cerebellar ataxia, Friedreich's ataxia merits separate consideration because it is the most common, and because of its unique clinical and pathologic features. Unlike most of the late-onset autosomal dominant spinocerebellar ataxias discussed above, Friedreich's ataxia begins in childhood. It is transmitted by autosomal recessive inheritance and is due to an expanded GAA trinucleotide repeat in a noncoding region of the **frataxin** gene on chromosome 9 (see Table 3-10). The recessive inheritance of Friedreich's ataxia suggests a loss-of-function mutation. Most affected patients are homozygous for the trinucleotide repeat expansion in the Friedreich's ataxia gene, but some are heterozygous, with the repeat affecting one allele and a point mutation on the other allele.

The pathologic findings are localized, for the most part, to the spinal cord. These include degeneration of the spinocerebellar tracts, posterior columns, and dorsal roots as well as depletion of the neurons in Clarke's column that are the cells of origin of the dorsal spinocerebellar tracts. Large myelinated axons of peripheral nerves and cell bodies of primary sensory neurons in dorsal root ganglia are also involved.

### **Clinical Findings**

Detailed clinical evaluation of relatively large numbers of patients has allowed certain diagnostic criteria to be established (Table 3-11). Clinical manifestations almost always appear after age 4 years and before the end of puberty, with more expanded repeats correlating with earlier onset.

The initial symptom is progressive gait ataxia, followed by ataxia of all limbs within 2 years. During the same early period, knee and ankle tendon reflexes are lost and cerebellar dysarthria appears; reflexes in the arms and in some cases at the knees may be preserved. Joint position and vibration sense are impaired in the legs, typically adding a sensory component to the gait ataxia. Abnormalities of light touch, pain, and temperature sensation occur less frequently. Weakness of the legs—and less often the arms—is a later development and may be of the upper or lower motor neuron variety (or both).

Extensor plantar responses usually appear during the first 5 years of symptomatic disease. Pes cavus (high-arched

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feet with clawing of the toes caused by weakness and wasting of the intrinsic foot muscles) is a widely recognized sign, but it may also be an isolated finding in otherwise unaffected family members. It is also a classic feature of other neurologic disorders, notably certain hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth disease). Severe progressive kyphoscoliosis contributes to functional disability and may lead to chronic restrictive lung disease. While cardiomyopathy is sometimes detectable only by echocardiography or vectorcardiography, it may result in congestive heart failure and is a major cause of morbidity and death.

Other abnormalities include visual impairment (usually from optic atrophy), nystagmus, paresthesias, tremor,

hearing loss, vertigo, spasticity, leg pains, and diabetes mellitus.

### **Differential Diagnosis**

Friedreich's ataxia can usually be differentiated from other cerebellar and spinocerebellar degenerations (see

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above) by its early onset and the presence of prominent sensory impairment, areflexia, skeletal abnormalities, and cardiomyopathy. A somewhat similar disorder may result from vitamin E deficiency. Cerebellar ataxia that begins in childhood can also be caused by ataxia-telangiectasia; the clinical features that distinguish Friedreich's ataxia from ataxia-telangiectasia are discussed below.

### **Prognosis**

No treatment is available, but orthopedic procedures such as tenotomy may help to correct foot deformities. Advances in antimicrobial therapy have altered the ultimate course of the disorder, so that cardiomyopathy has become more frequent and infection less frequent as a cause of death. Neurologic dysfunction typically results in the inability to walk unaided within 5 years after the onset of symptoms and in a bedridden state within 10–20 years. The average duration of symptomatic illness is about 25 years, with death occurring at a mean age of about 35 years.

## **8. Ataxia-Telangiectasia**

Ataxia-telangiectasia (also known as Louis-Bar syndrome) is an inherited autosomal recessive disorder with its onset in infancy. The disease results from mutations in the *ATM* gene, which has been localized to chromosome 11q22.3. Deletions, insertions, and substitutions have all been described and are presumed to represent loss-of-function mutations, consistent with the autosomal recessive inheritance of ataxia-telangiectasia. Although the abnormal gene product has not been identified, a defect in DNA repair is thought to be involved in pathogenesis. Ataxia-telangiectasia is characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, and immunologic deficiency. All patients suffer from progressive pancerebellar degeneration—characterized by nystagmus, dysarthria, and gait, limb, and trunk ataxia—that begins in infancy. Choreoathetosis, loss of vibration and position sense in the legs, areflexia, and disorders of voluntary eye movement are almost universal findings. Mental deficiency is commonly observed in the second decade; oculocutaneous telangiectasia usually appears in the teen years. The bulbar conjunctivae are typically affected first, followed by sun-exposed areas of the skin, including the ears, nose, face, and antecubital and popliteal fossae. The vascular lesions, which rarely bleed, spare the central nervous system. Immunologic impairment (decreased circulating IgA and IgE) usually becomes evident later in childhood and is manifested by recurrent sinopulmonary infections in more than 80% of patients.

Other common clinical findings are progeric changes of the skin and hair, hypogonadism, and insulin resistance. The characteristic laboratory abnormalities include those related to immunologic deficiency and elevation of  $\alpha$ -fetoprotein and carcinoembryonic antigen levels.

Because the vascular and immunologic manifestations of ataxia-telangiectasia occur later than the neurologic symptoms, the condition may be confused with Friedreich's ataxia, which also manifests in childhood (see above). Ataxia-telangiectasia can be distinguished by its earlier onset (before age 4 years), associated choreoathetosis, and the absence of such skeletal abnormalities as kyphoscoliosis.

There is no specific treatment for ataxia-telangiectasia, but antibiotics are useful in the management of infections and x-rays should be avoided because of the abnormal cellular sensitivity to ionizing radiation in this disorder.

## **9. Wilson's Disease**

Cerebellar symptoms may occur in Wilson's disease, a disorder of copper metabolism characterized by copper deposition in a variety of tissues. Wilson's disease is an inherited autosomal recessive disorder due to mutations in the *ATP7B* gene on chromosome 13q14.3–q21.1, which codes for the  $\beta$  polypeptide of a copper-transporting ATPase. Wilson's disease is discussed in more detail in Chapter 7.

## **10. Creutzfeldt-Jakob Disease**

Creutzfeldt-Jakob disease is described in Chapter 1 as a prion disease that causes dementia. Cerebellar signs are

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present in about 60% of patients, and the patients present with ataxia in about 10% of cases. Cerebellar involvement is diffuse, but the vermis is often most severely affected. In contrast to most other cerebellar disorders, depletion of granule cells is frequently more striking than Purkinje cell loss.

Patients with cerebellar manifestations of Creutzfeldt-Jakob disease usually complain first of gait ataxia. Dementia is usually evident at this time, and cognitive dysfunction always develops eventually. Nystagmus, dysarthria, truncal ataxia, and limb ataxia are all present initially in about half the patients with the ataxic form of Creutzfeldt-Jakob disease. The course is characterized by progressive dementia, myoclonus, and extrapyramidal and pyramidal dysfunction. Death typically occurs within 1 year after onset.

## 11. Posterior Fossa Tumors

Tumors of the posterior fossa cause cerebellar symptoms when they arise in the cerebellum or compress it from without. The most common cerebellar tumors of childhood are astrocytomas and medulloblastomas. Metastases from primary sites outside the nervous system predominate in adults (Table 3-12).

Type	Percentage of All Cerebellar Tumors	Percentage of Cerebellar Tumors in Adults ( $\geq 20$ years)
Metastasis	36	56
Astrocytoma	28	10
Medulloblastoma	16	9
Schwannoma	4	7
Hemangioblastoma	4	5
Meningioma	4	5
Ependymoma	2	1
Other	6	7

<sup>1</sup>Data from Gilman S, Bloedel JR, Lechtenberg R: Page 334 in: *Disorders of the Cerebellum*. Vol 21 of *Contemporary Neurology Series*. Davis, 1981.

**Table 3-12.** Tumors of the cerebellum.<sup>1</sup>

Patients with cerebellar tumors present with headache from the increased intracranial pressure or with ataxia. Nausea, vomiting, vertigo, cranial nerve palsies, and hydrocephalus are common. The nature of the clinical findings varies with the location of the tumor. Most metastases are located in the cerebellar hemispheres, causing asymmetric cerebellar signs. Medulloblastomas and ependymomas, on the other hand, tend to arise in the midline, with early involvement of the vermis and hydrocephalus.

As in the case of most brain tumors, the CT scan or—especially—MRI is extremely useful in diagnoses but biopsy may be required for histologic characterization. Methods of treatment include surgical resection and irradiation. Corticosteroids are useful in controlling the associated edema.

**Metastases**—from the lung and breast and less often from other sites—are the most common tumors of the cerebellum, especially in adults. The site of the primary tumor may or may not be evident at the time the patient presents with central nervous system involvement. If the site is not evident, careful examination of the breasts and skin, chest x-ray, urinalysis, and tests for the presence of occult blood in the stool may lead to a diagnosis. The prognosis for patients with cerebellar metastases is usually worse than for patients with supratentorial lesions. Patients with carcinoma of the breast tend to survive longer than those with primary lung tumors.

**Cerebellar astrocytomas** usually occur between the ages of 2 and 20 years, but older patients can also be affected. These tumors are often histologically benign and cystic in appearance. Symptoms of increased intracranial pressure, including headache and vomiting, typically precede the onset of cerebellar dysfunction by several months. If complete surgical resection is possible, cerebellar astrocytoma is potentially curable.

**Medulloblastoma** is common in children but rare in adults. It is believed to originate from neuroectodermal rather than glial cells. In contrast to astrocytomas, medulloblastomas tend to be highly malignant. They often spread through the subarachnoid space and ventricles and may metastasize outside the nervous system. Whereas most childhood medulloblastomas are located in the midline, adult-onset tumors usually arise laterally. Headache, vomiting, ataxia, and visual deterioration are common presenting symptoms. Hemiataxia is a frequent finding in adults because of the hemispheric location of most tumors. Gait ataxia, papilledema, nystagmus, facial palsy, and neck stiffness are also common. Without treatment, medulloblastoma causes death within a few months after presentation. Treatment with partial surgical resection, decompression, and craniospinal irradiation may prolong survival for years. Developing the tumors in adulthood and being female are favorable prognostic factors.

**Acoustic neuromas** have been discussed previously as a cause of vestibular nerve dysfunction. Growth of these or other less common tumors of the cerebellopontine angle may result in compression of the ipsilateral

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cerebellar hemisphere, causing hemiataxia in addition to the earlier symptoms of vertigo and hearing loss. These tumors are histologically benign and often fully resectable. Unilateral acoustic neuromas can occur in **neurofibromatosis 1** (von Recklinghausen's disease), whereas bilateral acoustic neuromas are characteristic of **neurofibromatosis 2**. These disorders are discussed in more detail in the section on cerebellopontine angle tumors (above).

**Hemangioblastoma** is a rare benign tumor that usually affects adults. It can be an isolated abnormality or a feature of von Hippel-Lindau disease. In the latter case, associated features include retinal hemangioblastoma; cysts of the kidney, pancreas, or other viscera; and polycythemia. Patients typically present with headache, and common examination findings include papilledema, nystagmus, and ataxia. Treatment is by surgical resection.

**Meningiomas of the posterior fossa** constitute 9% of all meningiomas. They are benign tumors, derived from arachnoidal cap cells, and involve the cerebellum indirectly by compression. The locations of posterior fossa meningiomas (in decreasing order of frequency) include the posterior surface of the petrous bone, the tentorium cerebelli, the clivus, the cerebellar convexities, and the foramen magnum. Meningiomas grow slowly and usually present with headache, although tumors of the cerebellopontine angle or clivus may come to attention when they give rise to cranial nerve or brainstem symptoms. Where possible, complete surgical resection is curative.

**Ependymomas** most commonly arise from the walls or choroid plexus of the fourth ventricle. Like medulloblastomas, they are malignant tumors that seed through the ventricular system and usually occur in children. Because of their location they produce early hydrocephalus; cerebellar signs caused by compression are late or minor manifestations. Surgical resection, craniospinal irradiation, and shunting procedures to relieve hydrocephalus may prolong survival, but widespread dissemination of the tumors and postoperative recurrences are common.

## 12. Posterior Fossa Malformations

Developmental anomalies affecting the cerebellum and brainstem may present with vestibular or cerebellar symptoms in adulthood. This occurs most commonly with type I (adult) **Arnold-Chiari malformation**, which consists of downward displacement of the cerebellar tonsils through the foramen magnum. The clinical manifestations of this malformation are related to cerebellar involvement, obstructive hydrocephalus, brainstem compression, and syringomyelia. Type II Arnold-Chiari malformation is associated with meningomyelocele (protrusion of the spinal cord, nerve roots, and meninges through a fusion defect in the vertebral column) and has its onset in childhood.

Cerebellar ataxia in the type I malformation usually affects the gait and is bilateral; in some cases it is asymmetric. Hydrocephalus leads to headache and vomiting. Compression of the brainstem by herniated cerebellar tissue may be associated with vertigo, nystagmus, and lower cranial nerve palsies. Syringomyelia typically produces a capelike distribution of defective pain and temperature sensation.

Arnold-Chiari malformation can be diagnosed by CT or MRI studies that demonstrate cerebellar tonsillar herniation. High cervical laminectomy with decompression of the posterior fossa may be of therapeutic benefit.

## SENSORY ATAXIAS

Sensory ataxia results from impaired proprioceptive sensation at the level of peripheral nerves or roots,

posterior

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columns of the spinal cord, or sensory pathways in the brain. Clinical findings include defective joint position and vibration sense in the legs and sometimes the arms, unstable stance with Romberg's sign, and a gait of slapping or steppage quality. Sensory ataxia can be produced by polyneuropathies that prominently affect large, myelinated sensory fibers (Table 3-13) and by myelopathies, including those resulting from Friedreich's ataxia, neurosyphilis (tabes dorsalis), or vitamin B<sub>12</sub> deficiency (Figure 3-16). Polyneuropathies, tabes dorsalis, and vitamin B<sub>12</sub> deficiency are discussed in detail in Chapter 6.

<p><b>Polyneuropathy<sup>1</sup></b>                  Autosomal dominant sensory ataxic neuropathy                  Cisplatin (<i>cis-platinum</i>)                  Dejerine-Sottas disease (HMSN<sup>2</sup> type III)                  Diabetes                  Diphtheria                  Hypothyroidism                  Immune-mediated neuropathies (GALOP syndrome, anti-MAG antibody syndrome, Miller Fisher syndrome, anti-GD1b antibody syndrome)                  Isoniazid                  Paraneoplastic sensory neuronopathy (anti-Hu antibodies)                  Pyridoxine                  Refsum's disease                  Taxol</p> <hr/> <p><b>Myelopathy<sup>3</sup></b>                  Acute transverse myelitis                  AIDS (vacuolar myelopathy)                  Multiple sclerosis                  Tumor or cord compression                  Vascular malformations</p> <hr/> <p><b>Polyneuropathy or myelopathy</b>                  Friedreich's ataxia                  Neurosyphilis (tabes dorsalis)                  Nitrous oxide                  Vitamin B<sub>12</sub> deficiency                  Vitamin E deficiency</p> <hr/> <p><sup>1</sup> Involving large, myelinated sensory fibers.  <sup>2</sup> Hereditary motor and sensory neuropathy.  <sup>3</sup> Involving posterior columns.</p>
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Table 3-13. Causes of sensory ataxia.

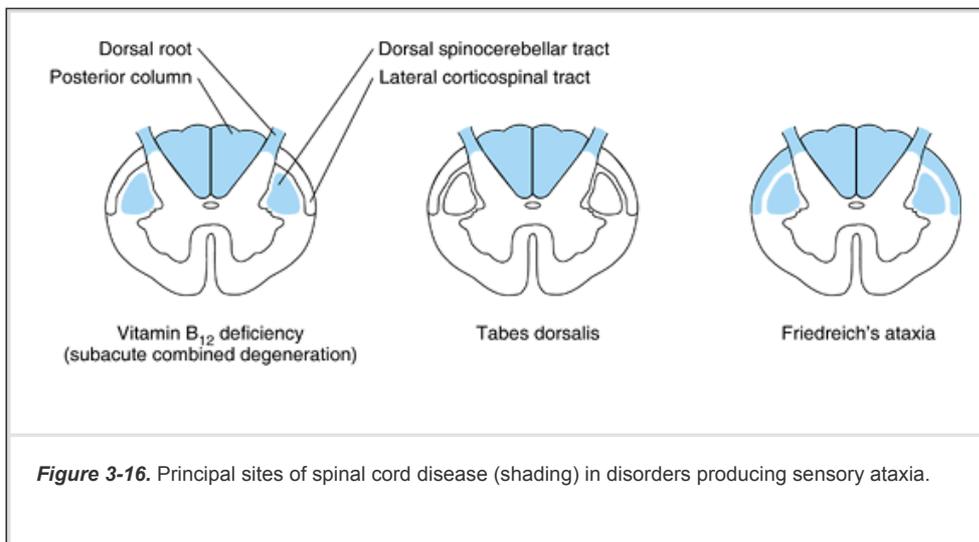


Figure 3-16. Principal sites of spinal cord disease (shading) in disorders producing sensory ataxia.

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