CHAPTER 19

Disorders of the Cerebellum and Its Connections

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- Signs and Symptoms of Cerebellar Damage
- Extracerebellar Causes of Cerebellar Signs and Symptoms
- Localization of Cerebellar Dysfunction
- Specific Etiologies

The cerebellum, which lies just dorsal to the pons and medulla, consists of two highly convoluted lateral cerebellar hemispheres and a narrow medial portion, the vermis. It is connected to the brain by three pairs of dense fiber bundles called the peduncles. Although the structure and function of the cerebellum have long been studied, the precise role of the cerebellum in motor control remains to be fully elucidated.

As discussed in Chapter 8, it is clear that the cerebellum receives a tremendous number of inputs from the spinal cord and from many regions of both the cortical and subcortical brain. In this way, the cerebellum receives extensive information from somesthetic, vestibular, visual, and auditory sensory systems, as well as from motor and nonmotor areas of the cerebral cortex. Although afferent connections outnumber efferent projections by about 40 to 1, the cerebellum has extensive outgoing connections to many areas of the brainstem, midbrain, and cerebral cortex.

It is evident that while the cerebellum does not serve to initiate most movement, it does interact with areas of the brain that do.\(^1\)\(^-\)\(^3\) In doing so, the cerebellum promotes the synchrony and accuracy of movement required for purposeful motor activity. The cerebellar modulation and coordination of muscular activity are important in skilled voluntary movement, as well as in the movements of posture and equilibrium.

The cerebellum is vulnerable to most of the nonspecific disease processes that affect other areas of the central nervous system, as well as to certain diseases unique to the cerebellum (Table 19-1). When the cerebellum or its direct connections are damaged, a characteristic constellation of symptoms and clinical signs arises. At first glance, the motor deficits produced by such damage are less than one might expect of a structure so centrally located in the neuraxis and so intimately involved in motor control. Extensive damage to the cerebellum, for example, does not abolish movement and rarely even causes muscle weakness. Somesthetic or other sensibilities are not disrupted, nor is cognition. Instead, the most prominent effects of cerebellar destruction are a type of incoordination or clumsiness.
Table 19-1. Cerebellar Disorders Organized by Etiology

- Inherited or idiopathic degenerations
- Nutritional disorders
- Neoplastic and paraneoplastic disorders
- Developmental disorders
- Disorders due to infection
- Vascular disorders
- Intoxications
- Physical or mechanical trauma
- Metabolic disorders
- Demyelinating or dysmyelinating disorders

of movement called ataxia and abnormal muscle tone. Although cerebellar lesions may delay the initiation of movements and alter their form, they do not prevent their execution. This is very different from the motor deficits that result from damage to the motor cortex or to the systems descending from it, in which the strength and speed of contraction are impaired and the ability to contract individual muscles may be lost altogether. If you recall that the role of the cerebellum is not to initiate motor activity but to modulate and refine motor behaviors initiated elsewhere, then the signs and symptoms of cerebellar damage are not surprising.

Destruction of small portions of the cerebellar cortex rarely causes detectable abnormalities in motor function. To cause serious and continuing dysfunction, the cerebellar lesion must be extensive and usually involves one or more of the deep cerebellar nuclei in addition to the cerebellar cortex. It is interesting that the neurologic signs produced even by extensive damage tend to gradually diminish with time, assuming that the underlying disease process does not itself progress. Such improvement is particularly evident following childhood damage. In experimental animals, even after as much as 50% of the cerebellar cortex has been removed, if the deep nuclei are left intact, motor function appears normal as long as the movements are performed slowly.

Signs and Symptoms of Cerebellar Damage

Although the specific neurologic signs associated with cerebellar disease and injury are numerous, the basic functional deficits producing these signs are relatively few (Table 19-2). Moreover, these basic functional deficits are a logical consequence of the disruption of the motor functions known to be carried out by the cerebellum.

Incoordination of Movement

The cerebellum is responsible for the smoothly integrated coordination of movements. It is needed for movements that require the concerted, synergistic contraction of multiple muscle groups, and it permits such movements to be carried out efficiently and accurately.

The most conspicuous and most common result of cerebellar dysfunction is an incoordination or clumsiness of movement. This incoordination is referred to by clinicians as ataxia, a term derived from the Greek word meaning “lack of order.” Patients with ataxia have difficulty regulating the force, range, direction, velocity, and rhythm of muscle contractions and in maintaining the synergy that normally exists among the various muscles involved in motor activities. Ataxia is a general term and may be manifested in any number of specific clinical signs, depending on the extent and locus of involvement. Limb movements, gait, speech, and eye movements all may be affected.
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Table 19-2. Basic Characteristics of Cerebellar Signs and Symptoms

- Lesions of the cerebellum produce errors in the planning and execution of movements, rather than paralysis or involuntary movements.
- In general, if symptoms predominate in the trunk and legs, the lesion is near the midline; if symptoms are more obvious in the arms, the lesion is in the lateral hemispheres.
- If only one side of the cerebellum is affected, the symptoms are unilateral and ipsilateral to the lesion.
- The most severe disturbances are produced by lesions in the superior cerebellar peduncle and the deep nuclei.
- Many of the symptoms of cerebellar disease improve gradually with time if the underlying disease process does not itself progress.
- Almost all patients with cerebellar lesions have some type of gait disturbance.
- Speech disturbances occur only with bilateral damage.
- Signs and symptoms similar to those produced by cerebellar lesions can appear with disorders that affect structures adjacent to the cerebellum or affect the afferent or efferent connections of the cerebellum.

If the legs and trunk are affected, difficulty in maintaining posture and coordinating leg movements will result in ataxia of gait. Such patients are unsteady during ambulation and attempt to improve their stability by walking with a broad-based gait and lower center of gravity. Their steps are uncertain and irregular, and they may stagger or veer from side to side. Patients with gait ataxia also have a decrease in the normal, free-flowing arm swing that normally accompanies ambulation. Walking heel-to-toe or running the heel of one foot down the shin of the other leg while seated or lying down is difficult and serves as tests for this deficit. Problems with standing or walking are present in almost all patients with cerebellar damage, regardless of the site of the damage, and, when severe, may cause considerable disability.

Ataxia of the arms (limb ataxia) creates its own specific clinical signs. Difficulty in bringing a limb smoothly and accurately to a specific target in space is called dysmetria. An involved limb may either overshoot (hypermetria) or undershoot (hypometria) its target. Complex movements, because of errors in the timing and sequencing of their component parts, may deteriorate into a series of successive simple movements, rather than one smooth, coordinated movement. This is termed decomposition of movement and is most evident in movements involving multiple joints. At the end of such movements, when the patient is attempting to achieve the greatest precision, a coarse tremor may develop called an intention tremor. These tremors do not occur at rest nor during postural fixation, but develop while precise, intentional movements are undertaken. Intention tremors probably reflect impaired coordination of agonists and antagonists, as well as an attempt to correct for overshoot and undershoot.

Dysmetria, decomposition, and tremor all can be demonstrated by simply asking the patient to point from one stationary target to another, such as in bringing the tip of the finger of the extended upper extremity to the nose (Fig. 19-1). As the movement is undertaken, each joint of the shoulder, elbow, wrist, and finger may flex independently in a puppetlike fashion and large errors in the direction and range of movement occur as the target is approached. As the finger nears the nose, the hand and finger exhibit a tremor. Limb ataxia may also be manifested as an impairment of the ability to perform rapidly alternating movements, such as rapid supination and pronation of the forearm. This is termed dysdiadochokinesia.

Persistent incoordination of axial muscles may lead to reversible abnormalities of stance and posture, such as head or body tilt, or to more permanent skeletal abnormalities, such as scoliosis. Truncal ataxia may result in swaying of the trunk, staggering gait, and difficulty in sitting unsupported.

Bulbar muscles may also be affected, leading to slurred speech (dysarthria) and numerous disturbances of oculomotor activity, including nystagmus.
Muscle tone refers to the ease with which a muscle may be lengthened by passive stretch. The normal cerebellum contributes to the maintenance of muscle tone through facilitatory influences on skeletal muscle stretch reflexes. Cerebellar output increases gamma input to muscle spindles, making them more sensitive to stretch and thus increasing overall muscle tone. Without this input, tone diminishes.

Hypotonia refers to a decreased resistance to passive stretch as might occur with passive limb movement. Although not as common as ataxia, hypotonia may result from cerebellar damage and lead to a number of distinct clinical signs. Hypotonia is most evident shortly after acute cerebellar injury and tends to decrease with time. In early and severe cases, a distinct flabbiness of muscle can be palpated and the muscle accommodates greater stretch without discomfort. Decreased muscle tone may result in a pendular limb, with pendular deep tendon reflexes. For example, when the patellar reflex is elicited, the leg will continue to swing back and forth in a pendular fashion. Hypotonia is often associated with an inability to stop a rapidly moving limb (i.e., lack of check), resulting in an overshoot, followed by excessive rebound in the opposite direction. If such a patient is asked to pull upward strongly with his or her arm while the clinician first holds it back and then releases it, the arm will fly back, unchecked, until it strikes the face instead of being automatically stopped.

Although hypotonia is not as conspicuous as ataxia, it can exacerbate the symptoms produced by ataxia. Decreased tone in postural muscles, for example, contributes to gait disturbances and postural asymmetry. Hypotonia in the muscles of speech promotes abnormalities in pitch and loudness, and in oculomotor muscles results in difficulty in maintaining the gaze.
Dysequilibrium and Vertigo$^{1,2,4,5}$

The most primitive parts of the cerebellum (the flocculonodular lobes) have extensive connections with both the vestibular nuclei and the vestibular apparatus. It is likely that even in the human, the cerebellum plays a significant role in the maintenance of equilibrium and the coordination of head and eye movements.

Lesions in these regions result in disturbances of equilibrium that are particularly evident during rapid changes in body position or in the direction of movement. Patients may exhibit unsteadiness of gait or an inability to sit or stand without swaying or falling, as well as abnormalities of head posture and eye movement (nystagmus). These deficits are specifically related to an inability to carry out motor activities against the force of gravity. The principal defect is in equilibrium, not ataxia or abnormal muscle tone. Moreover, cerebellar infarction and hemorrhage (stroke) have been shown to induce signs and symptoms such as vertigo, nausea, vomiting, and nystagmus, which mimic damage done to the vestibular labyrinth itself.

Delays in the Initiation and Termination of Movement$^{1,2,4,5}$

Lateral portions of the cerebellar hemispheres and the associated dentate nuclei play important roles in the planning and programming of movement. This is particularly so in multijoint movements and in those requiring fine dexterity in the distal extremities. Lesions on either side of the dentate nuclei or the overlying cortex can interfere with this programming, resulting in delays in both the initiation and the termination of movement. Intentional movements, such as grasping or pointing, may be slowed in both the buildup and the relaxation of force. Consequently, the movement of an affected limb is delayed and slowed.

Nonmotor Deficits

Although the principal physiologic importance of the cerebellum resides in its contributions to somatic motor control, evidence is accumulating that the cerebellum is also involved in a variety of nonmotor functions (see Chapter 8).

If this involvement is functionally significant, one would expect evidence of this involvement to appear among the sequelae of cerebellar damage. In fact, nonmotor deficits are now beginning to be discussed in the context of human cerebellar disease. Studies conducted in both animals and humans provide evidence that the cerebellum plays a role in motor learning.$^{8,9}$ Experimental cerebellar lesions in animals and pathologic lesions in humans seem to interfere with these learning processes.$^{10-12}$ Evidence is also accumulating through the use of active imaging techniques that the cerebellum is engaged in such mental functions as shape and word recognition.$^{13,14}$ Although an association between some developmental disorders of the cerebellum and retarded intellectual development has been reported for some time,$^{15}$ cognitive abnormalities are not usually apparent in patients with cerebellar disease. Recently, subtle defects in verbal and nonverbal intelligence, in memory, and in other "higher functions" in cerebellar patients have been reported.$^{16-18}$ Although anatomic connections exist between the cerebellum and the areas of the brain involved in the expression of emotion and although animal experiments suggest involvement of the cerebellum in various emotion-laden behaviors such as rage, fear, and aggression, little is known of the role the cerebellum may play in mediating or influencing emotions in humans. In this regard, specific structural abnormalities in the cerebellum of patients with autism$^{19-21}$ and certain psychological disorders have been revealed by computed tomography (CT) and magnetic resonance imaging (MRI) scans, as well as by pathologic study.$^{22-24}$ As clinical skills and neuroimaging techniques are refined and more attention is focused on nonmotor deficits, these deficits will undoubtedly be found within the constellation of findings associated with cerebellar dysfunction.
Extracerebellar Causes of Cerebellar Signs and Symptoms

Many of the signs and symptoms associated with cerebellar damage can also be caused by lesions outside the cerebellum itself. Ataxia, for example, can be caused or exacerbated by a variety of extracerebellar lesions. Conditions that disrupt the spinocerebellar tracts can cause dysmetria and ataxia by depriving the cerebellum of proprioceptive input. These kinds of defects underlie Friedreich's ataxia (discussed later in this chapter) and many of the cerebellar findings of multiple sclerosis (see Chapter 22). By the same token, disruption of somatosensory nerves in the peripheral nervous system can impair the proprioceptive sense enough to cause a sensory ataxia, such as might be observed in alcoholic or other types of peripheral neuropathy (see Chapter 15). Disorders of the vestibular system, by interfering with balance and equilibrium, can mimic and exacerbate the gait problems associated with cerebellar damage.

Localization of Cerebellar Dysfunction

As discussed in Chapter 8, attempts have been made to functionally compartmentalize the cerebellum into three basic regions, using either phylogenetic or neuroanatomic criteria (Fig. 19-2). Although not totally congruent, the archicerebellum, paleocerebellum, and neocerebellum of the phylogenetic scheme correspond fairly well to the vestibulocerebellum, spinocerebellum, and cerebrocerebellum, which are defined by their primary afferent and efferent connections. Attempts have been made over the years to organize the various signs and symptoms that arise from cerebellar disease into distinct syndromes, which reflect the region of the cerebellum that is damaged. Accordingly, three syndromes have been described, which some consider to be useful models for localizing cerebellar dysfunction.

Vestibulocerebellar, Archicerebellar, or Flocculonodular Lobe Syndrome

The flocculonodular lobe is phylogenetically the oldest division of the cerebellum and receives extensive input from the vestibular system. This is why this portion of the cerebellum is often termed the archicerebellum or vestibulocerebellum. The vestibulocereb-
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The cerebellum receives mossy fiber input chiefly from the vestibular nerve and nuclei and projects back to the vestibular nuclei, which in turn project to the spinal cord (vestibulospinal tracts) and the oculomotor nuclei. This system is important for equilibrium and for control of the axial muscles that are used to maintain balance in the face of gravity. The vestibulocerebellum also controls eye movement and coordinates movements of the head and eyes. Because of the close relationship between the vestibulocerebellum and the vestibular system, damage to this region of the cerebellum causes clinical findings that mimic vestibular disease itself. Such disorders cause disturbances of locomotion and equilibrium, with prominent truncal and gait ataxia. Patients with isolated flocculonodular lesions lose their ability to stand or walk without swaying or falling and tend to fall even when sitting with their eyes open. It is interesting that when the effects of gravity are reduced by the patient lying in bed or being physically supported, movements may be completely normal. Abnormalities of posture and station (e.g., head tilt) and of eye movements also occur. Tremor is not evident and muscle tone remains normal.

The most common lesion involving the vestibulocerebellum is a special type of tumor, a medulloblastoma, which usually occurs in children.

Spinocerebellar or Paleocerebellar Syndrome

Most of the vermal and paravermal (intermediate) regions of the cerebellum receive extensive somatosensory input from the spinal cord and are thus called the spinocerebellum. The spinocerebellum also receives input from the auditory, visual, and vestibular systems. The vermal and intermediate portions of the spinocerebellum project to different deep nuclei, controlling different components of the descending motor pathways. The vermis projects to the fastigial nucleus and from there influences cortical and brainstem components of the medial descending systems (axial and girdle muscles). The intermediate part of the cerebellar hemispheres projects to the interposed nucleus to control the lateral descending systems (distal muscles of extremities). The spinocerebellum receives a continuous flow of somatosensory information regarding the status of the musculoskeletal system, as well as concurrent information from cortical areas about motor commands. It uses this feedback to monitor and refine the execution of movement and to control muscle tone.

Discrete lesions limited to the spinocerebellum, such as those described in experimental animals, seldom occur in humans. Damage to the human spinocerebellum is most commonly seen in the context of a late degeneration and atrophy of the anterior lobes associated with chronic alcoholism and thiamine deficiency. The cardinal feature of spinocerebellar disease is involvement of the legs, resulting in abnormal gait and stance. The gait is wide-based and ataxic, with small hesitant steps. The gait ataxia of spinocerebellar damage is different from that arising from vestibulocerebellar (flocculonodular) damage. Spinocerebellar ataxia reflects a more general deficit in the control of the muscles of ambulation, whereas vestibulocerebellar ataxia reflects a particular inability to control the leg muscles in the presence of the force of gravity. In the case of spinocerebellar damage, the ataxia is not relieved when the patient is freed from the effects of gravity by being physically supported or lying in bed, as it would be with vestibulocerebellar damage.

Cerebrocerebellar, Neocerebellar, or Lateral Cerebellar Syndrome

The cerebrocerebellum, which occupies the lateral zone of the cerebellar hemispheres, is phylogenetically late in developing and is particularly well developed in primates. This region receives most of its input from sensory, motor, and premotor areas of the cerebral cortex that project to the cerebrocerebellum via the pontine nuclei. Most of the output of this area is to the dentate nucleus, which in turn projects back to the cerebral cortex. Through its extensive connections with the cerebral cortex, the cerebrocerebellum
is thought to function in the planning and initiation of voluntary movements. It is necessary for achieving precision in rapid limb movements, especially those involving fine dexterity of the distal extremities and movement at multiple joints. Damage to the lateral hemispheres and dentate nuclei disturbs skilled coordinated movements and speech. Errors in direction, deviation from proper course, dysmetria, dysdiadochokinesia, and intention tremor all may be present, especially in movements of the upper extremities. The gait may actually be normal, reflecting the relative sparing of the axial muscles and lower limbs. Intentional movements, such as grasping or pointing, may be delayed in their initiation and slowed in both the buildup and the relaxation of intended force. Stretch reflexes and muscle tone are often diminished, resulting in flabbiness, lack of check, and pendular deep tendon reflexes. Muscle weakness and fatigability, although not that common in cerebellar disorders, are most prominent in cerebrocerebellar syndrome. Dysarthric speech may occur with bilateral involvement and can be pronounced. Oculomotor signs may also occur.

When the damage is unilateral, the ipsilateral limb is affected. With limited damage, it is sometimes possible to show impairment only of highly trained movements, such as playing a musical instrument, whereas all other movements appear normal.

Problems with Localization of Dysfunction

Although the divisions of the cerebellum that are based on phylogenetic criteria and comparative anatomic studies (e.g., the archicerebellum, paleocerebellum, and neocerebellum) correspond reasonably well to the divisions of the cerebellum defined by the locus of the termination of the major afferent projections (e.g., the vestibulocerebellum, spinocerebellum, and cerebrocerebellum, respectively). This congruence is not total. Considerable overlap exists between the regions defined by the anatomic sites of afferent terminations. Moreover, the physiologic effects of activating afferent sources project far beyond the boundaries ascribed to these regions. Accordingly, some authors feel that it is misleading to define the clinical scenarios arising from cerebellar damage in terms of these phylogenetic or neuroanatomic regions.

In addition, it should be recognized that many symptoms of cerebellar dysfunction simply defy limitation to any one division of the cerebellum. A good example of this is disturbance of gait, which is the most common deficit seen in cerebellar disease. Gait may be disturbed as a consequence of the impairment of equilibrium encountered in disorders involving the flocculonodular lobes. Gait impairment may also result from anterior lobe disorders that adversely affect postural control. Finally, posterior lobe lesions can disturb gait through effects on muscle tone and volitional movement. Accordingly, gait disturbance is to be expected with practically all cerebellar lesions and by itself does little to localize the site of cerebellar damage. In addition, gait can be impaired by disorders of the spinal cord or peripheral nerves that disrupt the flow of proprioceptive information to the cerebellum, as well as by damage to the vestibular system. Lesions in certain cerebral and brainstem areas may likewise interrupt the flow of information to or from the cerebellum, causing gait disturbance similar to that seen in disease of the cerebellum itself.

Specific Etiologies

Although cerebellar disorders as a whole are not very common, a wide variety of factors, both inherited and acquired, can adversely affect cerebellar function (see Table 19–1). As with any region of the central nervous system, these conditions may be organized or classified using a number of different criteria, such as prominent clinical features, pathologic criteria, or etiologic factors. For the purposes of this discussion, the major
cerebellar disorders are organized along the lines of what is known of their etiology or pathogenesis. It should be noted that because of our incomplete understanding of the causes of many of these disorders, this classification scheme is somewhat arbitrary. Moreover, disorders may logically fall into more than one category.

**Inherited or Idiopathic Degenerations**

For unknown reasons, certain regions of the nervous system are particularly vulnerable to degenerative disease. Among these are the cerebellum and its connections. Many of these disorders are genetic or of unknown etiology. These may be distinguished from other degenerative conditions in which underlying toxic, metabolic, infectious, or neoplastic conditions have been identified. These are discussed elsewhere in this chapter.

The genetic and idiopathic degenerations constitute a large group of chronic disorders in which progressive ataxia, disintegration of gait, and dysarthria are the most prominent features. This is a complex group of disorders, and numerous attempts have been made to make order of their diversity. Classification schemes have been proposed, based on various clinical, pathologic, biochemical, and genetic criteria. Unfortunately, because of our limited understanding of etiologic factors, the variability of clinical features, and the poor correlation between clinical presentations and pathologic findings, none of these schemes is entirely satisfactory. It is often difficult to discern where one disorder ends and another begins. A more reliable classification of these disorders ultimately depends on a better understanding of the genetics of these disorders and the specific biochemical defects to which they give rise.

Nonetheless, for our descriptive purposes these degenerative diseases may be arbitrarily divided into large clinicopathologic groupings. The entire cerebellar system is vulnerable; one way to organize these disorders is to divide them into those with a predilection for the cerebellum itself and those with a predilection for the pathways to which it is connected. With respect to the latter, both peripheral and spinal neurons may be affected. Disorders that primarily involve the peripheral nerves, such as the hereditary sensory motor neuropathies, are discussed in Chapter 15; those with prominent involvement of the spinocerebellar tracts are discussed below. In either case, disruption of the flow of somatosensory (proprioceptive) information to the cerebellum can result in an incoordination of movement. These anatomic distinctions are somewhat arbitrary and although involvement of one particular part of the cerebellar system may be predominant, other regions may also be involved, particularly with disease progression.

**Spinal Ataxias**

In spinal ataxias the pathology involves primarily the spinocerebellar tracts, whereas the cerebellum itself and the brainstem are relatively spared. Associated degenerative changes in the peripheral nervous system may or may not be evident.

**Friedreich's Ataxia**

Friedreich's ataxia is one of the most common hereditary disorders of the nervous system. It is also the most common of the early-onset hereditary spinal ataxias, accounting for at least 50% of these disorders. The symptoms begin to develop in children between 8 and 15 years of age, with clumsiness of gait being the most common presenting symptom. As the condition develops, it is characterized by relentlessly progressive ataxia, with increasing weakness, loss of tendon reflexes, and impaired proprioceptive sensation in the lower limbs. The ability to walk is usually lost within 15 years of onset. Ataxia, which begins in the lower limbs, later becomes evident in the arms and then the trunk. Scoliosis is frequent and may be severe, particularly if the onset is early (Fig. 19–3). This deformity contributes to
eventual cardiopulmonary problems. Foot deformities, especially pes cavus, are also common. Ocular movements are almost always abnormal, and many patients develop a cerebellar-type dysarthria. Cardiomyopathy with abnormal electrocardiogram (ECG) findings is present in most patients with Friedreich's ataxia, and death from heart failure often occurs late in the disease.

Characteristic pathologic changes are observed in both the peripheral and central nervous systems, particularly in the sensory systems. In the peripheral nervous system, there is degeneration of sensory fibers, sensory ganglion cells, and posterior roots. In the central nervous system, the most conspicuous lesions are in the spinal cord, the posterior columns, and spinocerebellar tracts (Fig. 19-4). Although there may be some patchy loss of cerebellar Purkinje cells and mild degenerative changes in cerebellar nuclei, the ataxia of movement is largely a result of the loss of proprioceptive sense.

The condition most likely to be confused with Friedreich's ataxia is the peroneal atrophy syndrome, in which distal wasting and weakness of the lower limbs (and to a lesser degree the upper limbs) are associated with areflexia. This clinical syndrome is associated with type I hereditary sensory and motor neuropathy (see Chapter 15) and distal spinal muscular atrophies (see Chapter 16). In sporadic cases without skeletal deformity, distinguishing between Friedreich's ataxia and multiple sclerosis may also be difficult.
Cerebellar Ataxias

In the cerebellar ataxias, the predominant pathologic changes occur in the cerebellum and its immediate connections, rather than in the spinal cord tracts.

Olivopontocerebellar Atrophy

In this category are a number of similar disorders characterized by a combined degeneration of the cerebellum, pons, and inferior olives. In general, these disorders are characterized by progressive ataxia with a later onset than Friedreich's ataxia (e.g., between the third and fifth decades of life). The gait is affected first, with progressive ataxia of the trunk and limbs, impairment of equilibrium, slowness of voluntary movement, and abnormal speech. Although patients often have a pure cerebellar syndrome during the first few years of their illness, pyramidal tract signs, autonomic disturbances, and parkinsonian features with mild dementia may develop later in the illness. Autonomic disturbances may present as urinary incontinence or orthostatic hypotension. Considerable clinical variability exists among cases of olivopontocerebellar atrophy. Some patients present a picture of relatively pure cerebellar ataxia indistinguishable from that seen in patients with atrophy limited to the cerebellar cortex. Others may have more prominent parkinsonian features and an early dementia.

Pathologic changes are widespread, giving rise to the diverse clinical findings associated with this syndrome. Gross shrinkage of the pons and medulla may be evident, whereas neuronal loss in the inferior olives, cerebellar cortex, and basal ganglia is revealed by microscopic examination. Some degenerative changes may also be evident in the long motor tracts of the spinal cord and the anterior horn cells.
Attempts have been made to define various subtypes of this degeneration, based on the particulars of the mode of inheritance and the predominant clinical features; however, these explorations are beyond the scope of this discussion.

**Pure Cerebellar Degeneration**

In some instances, a relative pure cerebellar syndrome arises, reflecting pathologic changes restricted to just the cerebellum. Unlike Friedreich's ataxia and other spinocerebellar ataxias, there is little evidence of spinal cord involvement. Also, unlike olivopontocerebellar degeneration, there is no prominent involvement of other regions of the brain or brainstem. Although pure cerebellar degeneration can occasionally occur sporadically, in most cases it is evidently inherited as an autosomal-dominant trait. This disorder is less common than Friedreich's ataxia. Its age of onset is later, usually occurring in the fourth decade of life or beyond. The patient first develops gait ataxia (with abnormal stance and instability of gait), progressing to dysarthria and finally to ataxia of the upper extremities and trunk. This disorder is progressive, but may be so gradual that incapacitation does not occur for decades and does not appreciably shorten the life span.

Pathologic changes include a marked loss of neurons (especially Purkinje cells) from the cerebellar cortex, most prominent on the superior surface of the vermis and adjacent parts of the cortex. In advanced cases, atrophy of the cerebellar cortex may be readily apparent with CT scanning. The deep cerebellar nuclei are relatively normal.

**Ataxia-Telangectasia**

Ataxia-telangectasia is the most common cerebellar ataxia of infancy and childhood. This inherited disorder is unusual to the extent that the cerebellar deficits are accompanied by characteristic vascular lesions (telangectasia) and recurrent pulmonary infections. The first motor symptom is usually truncal ataxia, which is noted when the child first begins to walk, resulting in an awkward, unsteady gait. When the child reaches 4 or 5 years of age, the limbs become ataxic and dysarthria may be evident. With progression of the disease, extrapyramidal signs such as dystonia and choreoathetosis may develop. Telangectasia is a vascular lesion formed by the dilatation of a small group of blood vessels, which is often observed as a "birthmark." For reasons unknown, these lesions develop in the skin or conjunctiva of the eye in this disorder.

Pathologic changes are noted in many regions of the nervous system, including a severe loss of Purkinje cells in the cerebellum, as well as atrophy of the posterior columns and spinocerebellar tracts of the spinal cord. Degenerative changes may also be evident in anterior horn cells, sensory and autonomic ganglia, and peripheral nerves.

**Nutritional Disorders**

Adequate nutrition is necessary for both the normal development and ongoing functioning of the entire nervous system. Nutritional disorders, particularly certain vitamin deficiencies, can adversely affect both the peripheral and central nervous systems, creating a wide range of neurologic manifestations. Depending on the deficiency, such findings may include changes in mental status (e.g., coma, mental retardation, psychosis), seizures, cerebellar ataxias, and peripheral motor and sensory disturbances. The few conditions in which cerebellar signs and symptoms are most prominent will be discussed in the following text.
Of all the vitamin deficiencies, thiamine deficiency is probably the most common in Western society and produces the most severe cerebellar deficits. This deficiency is most often seen in association with chronic alcoholism, but may also be seen in patients with abnormal gastrointestinal activity.

Chronic alcoholics frequently develop a condition termed the Wernicke-Korsakoff syndrome. Wernicke's disease is characterized by oculomotor abnormalities, altered mental status, and ataxia of stance and gait. This disease is often associated with Korsakoff's psychosis, a cognitive disorder in which short-term memory is impaired out of proportion to other intellectual functions.

Prominent cerebellar dysfunction occurs in about one third of all alcoholics, and is prominent among those with Wernicke's disease. Stance and gait are primarily affected, the legs being more affected than the trunk or arms. The ataxia may be so severe in the acute stage of the disease that the patient cannot walk or stand without support. Less severe degrees of the disease are characterized by a wide-based stance and slow, tentative steps. Speech disturbances and abnormal eye movements are relatively infrequent. Pathologic changes in the cerebellum consist of degeneration throughout the cortex, with a striking loss of Purkinje cells. This is most pronounced in the anterior superior aspects of the cerebellum (Fig. 19–5). Signs of peripheral neuropathy are found in most patients with Wernicke-Korsakoff syndrome, but in most cases involvement is mild and does not account for the gait disturbance.

Despite the well-known acute affects of alcohol directly on the cerebellum, it is generally thought that the chronic cerebellar syndrome observed in alcoholics is caused by thiamine deficiency rather than toxicity of the alcohol itself. Alcoholics with this...
condition are almost always malnourished. That this is not due to alcohol toxicity itself is further suggested by the facts that the ataxia may develop during periods of abstinence, that the symptoms can be relieved by administration of thiamine alone, and that an identical cerebellar degeneration may occur in other (nonalcoholic) states of poor nutrition.

A cerebellar cortical degeneration may also occur in malnourished alcoholics, which is distinct from that associated with Wernicke-Korsakoff syndrome. Truncal instability is the major symptom, often with incoordination of leg movements. The symptoms of this cerebellar degeneration may evolve over weeks or months and may eventually stabilize, even with continued drinking and poor nutrition. In Wernicke's disease, on the other hand, the symptoms are more likely to appear abruptly.

Alcoholics may also develop a sensorimotor polyneuropathy that stabilizes or improves with abstinence and an adequate diet. Although this neuropathy is found in most patients with Wernicke-Korsakoff syndrome, it more often occurs alone. As discussed in Chapter 15, this polyneuropathy is characterized by degeneration of both axons and myelin.

**Vitamin B<sub>12</sub> (Cobalamin) Deficiency<sup>5,39,40</sup>**

Vitamin B<sub>12</sub> deficiency, which is due to an inability to absorb this vitamin from the gut rather than dietary deficiency, produces a condition called *pernicious anemia*. The spinal cord, brain, optic nerves, and peripheral nerves all may be involved in pernicious anemia. The spinal cord is affected first and most often and reveals a diffuse degeneration of the white matter. Sensory disturbances, muscle weakness, and spastic ataxia are common. Paresthesias and decreased vibratory and position sense reflect lesions in both spinal and peripheral sensory pathways. Muscle weakness, spasticity, and abnormal tendon reflexes result from lesions in corticospinal tracts. Ataxia of gait and limbs probably reflects degeneration of spinocerebellar tracts and thus impairments of sensory feedback to the cerebellum.

**Vitamin E Deficiency<sup>5,29,30,39,40,46,47</sup>**

Vitamin E, a highly fat-soluble vitamin, is essential for normal neurologic function. Severe and prolonged vitamin E deficiency produces spinocerebellar degeneration in a number of inherited and acquired disorders. The most severe vitamin E deficiency state that occurs in humans is due to an inherited failure to synthesis apoprotein B, which is necessary for the intestinal absorption of fat. The result is extremely low levels of circulating lipids and fat-soluble vitamins. Serum vitamin E may be undetectable from birth. Patients with vitamin E deficiency may present in adolescence with progressive ataxia, areflexia, and proprioceptive loss, reflecting the degeneration of posterior column and spinocerebellar tracts in the spinal cord and a loss of large myelinated fibers in the peripheral nervous system. Vitamin E deficiency and similar neurologic symptoms may also occur in patients with diseases affecting bile salt concentrations in the small intestine or disturbing the absorptive surface of the gut.

**Neoplastic and Paraneoplastic Disorders**

Neoplastic disease, whether located within or near the cerebellum, or at some distant site, can adversely affect cerebellar function.

**Paraneoplastic Cerebellar Degeneration<sup>5,29,30,48–51</sup>**

All areas of the nervous system are susceptible to the deleterious effects of systemic carcinoma. In addition to effects on the cerebellum, neoplasm may cause encephalopathy, peripheral neuropathy, myopathy, and defects of neuromuscular transmission (e.g., Lambert-Eaton myasthenic syndrome; Chapter 14). A nonmetastatic paraneoplastic degeneration of
the cerebellar cortex is the most common paraneoplastic syndrome that affects the central nervous system. Symptoms may develop before or after discovery of the tumor. They usually begin with gait ataxia and over a few days or weeks progress to severe truncal and limb ataxia, with dysarthria and often with abnormal ocular movements. Vertigo is common and patients frequently complain of diplopia. Symptoms may progress in severity for several weeks or months and then stabilize. Unfortunately, by this stage, the patient may already be severely disabled. Often superimposed upon the cerebellar deficits are manifestations of a more diffuse paraneoplastic encephalopathy, including cognitive deterioration, bulbar palsy, and limb weakness.

Pathologic examination usually reveals a severe loss of Purkinje cells throughout the cerebellum, with or without evidence of inflammation. Some patients may have more widespread pathologic findings, including degeneration of spinocerebellar tracts, dorsal columns, and corticospinal tracts. Although the pathogenesis of paraneoplastic cerebellar degeneration is poorly understood, theories proposed to explain these remote effects of malignancy focus on nutritional deficiency, viral infections, and autoimmune mechanisms. Evidence such as clinical improvement with plasmapheresis and the presence of anti-Purkinje cell antibodies supports the notion of disturbed immune activity. The neurologic status of these patients can improve markedly with treatment of the underlying neoplasm.

Paraneoplastic cerebellar degeneration occurs most often in association with lung, breast, or ovarian cancer or Hodgkin's disease. Up to 50% of all patients over the age of 40 presenting with degenerative cerebellar disease may have an underlying neoplasm.

**Primary Tumors**

The cerebellum and adjacent structures may also constitute the site of primary tumor development. Posterior fossa tumors represent about one third of all intracranial tumors in adults and about two thirds in children. As with other regions of the central nervous system, these tumors may arise from either glial cells (e.g., astrocytomas) or neural cells (e.g., medulloblastomas). No particular type predominates in adults, but in children, most are astrocytomas or medulloblastomas. Lesions limited to just the cerebellum are rare, but are most often due to the presence of a discrete tumor. Cerebellar signs may occur with tumors of the cerebellum itself or with those arising in the fourth ventricle or brainstem.

As with any posterior fossa mass, nonspecific signs and symptoms reflecting increased intracranial pressure or compression of the brainstem may also develop. Headache, nausea, and vomiting may be accompanied to a variable extent by cranial nerve deficits, pyramidal tract signs, sensory disturbances, and decreasing consciousness. An expanding cerebellar mass may compress the medulla and portions of the cervical spine to the extent that infarction occurs and life-threatening abnormalities of cardiovascular and respiratory regulation ensue.

Tumors of the cerebellopontine angle, although they may be considered extracerebellar, are not an uncommon neoplastic cause of cerebellar signs. These tumors damage the inferior cerebellar peduncle, and the usual resulting complaints are impaired balance, ataxia, vertigo, and specific cranial nerve deficits (e.g., hearing loss, oculomotor disturbances, and facial paralysis). The most common tumors in this area are acoustic neuromas, which develop in the vestibulocochlear nerve.

**Metastatic Disease**

In adults, metastasis is the most common source of neoplasia in the posterior fossa (Fig. 19-6). Common primary tumor sites include the lung (about 50%), followed by the breast, kidney, and melanoma. The effects on the cerebellum reflect the location and extent of involvement. Focal neurologic deficits include limb or truncal ataxia or cranial nerve dysfunction. More generalized symptoms such as headache, nausea, or vomiting may result from obstructive hydrocephalus and elevated intracranial pressure.
Developmental Disorders$^5,29,30,58–62$

Congenital structural anomalies of the cerebellum are not uncommon and probably reflect both genetic (familial) and teratogenic factors. The cerebellum has the longest period of embryologic development of any major structure of the brain and is consequently vulnerable to teratogenic insults longer than most parts of the nervous system. The developing cerebellum is susceptible to the toxic effects of many drugs, chemicals, viral infections, radiation, and ischemic-hypoxic insults.

Malformation of the cerebellum may be focal, confined to the cerebellum, or associated with other brainstem or cerebral abnormalities. Congenital hypoplasia or even the absence of some or most of the cerebellum may occur. Because the vermis forms after the hemispheres, it is more likely to be absent or underdeveloped than other parts of the cerebellum. Although ataxia, hypotonia, tremor, and abnormal eye movements may be present, marked cerebellar hypoplasia has been shown by imaging studies and autopsy to be present in totally asymptomatic individuals (Fig. 19–7). A number of other malformations of the cerebellum have been described. The Dandy-Walker malformation consists of a ballooning of the posterior half of the fourth ventricle and hypoplasia of the cerebellar vermis.$^{60,61}$ Swelling of the brain due to excessive cerebrospinal fluid (hydrocephalus) almost always develops and accounts for many of the accompanying clinical manifestations. Hypotonia, cerebellar deficits, pyramidal signs, and seizures are present to varying degrees in about 25% of these cases. The Chiari malformations (the most common developmental abnormality of the posterior fossa) encompass a group of anomalies of the brainstem and cerebellum, in which there is a herniation of part of the cerebellum, medulla, and sometimes...
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Figure 19-7. Congenital Aplasia of the Left Cerebellar Hemisphere. The left hemisphere was almost totally lacking in this brain of an asymptomatic adult. (From Dow, Kramer, and Robertson, p 95, with permission.)

the pons through the foramen magnum into the upper cervical spinal canal. By compressing the cerebellum, lower brainstem, and cervical cord, this herniation may compromise neural function. The Chiari malformations are frequently associated with other malformations of the nervous system, such as spina bifida and hydrocephalus.

Perinatal hypoxia may produce severe cerebellar cortical atrophy; but signs of cerebellar dysfunction are usually overshadowed by evidence of damage to the cerebral cortex and other areas of the brain.

Disorders Due to Infection

A variety of organisms can infect the central nervous system, and in certain infectious disorders cerebellar signs and symptoms may be preeminent. Both slow and conventional viruses may produce a cerebellar syndrome. Creutzfeldt-Jakob disease, for example, is an encephalopathy resulting from infection with a so-called slow virus. It is now thought that almost 50% of affected patients may have a cerebellar or ataxic form of this disease, in which cerebellar deficits dominate the clinical picture for the first several months. Encephalitis produced by a wide range of conventional viruses can also give rise to cerebellar findings. Viral cerebellitis has been associated with polio, mumps, rubella, chickenpox, and herpesviruses. The most common cerebellar syndrome attributed to viral infection is an acute cerebellar ataxia that occurs in young children. Children may develop over hours or a few days severe truncal ataxia, with less prominent limb involvement. Recovery is usually complete, although it can take up to 6 months. Bacteria, fungi, and other parasites may also infect the cerebellum. Cerebellitis may accompany bacterial meningitis or be secondary to a variety of systemic bacterial infections. Atactic syndromes, in association with meningitis or systemic bacterial infection, are usually transient and resolve within weeks. Cerebellar syndromes as a sole result of fungal infection are rare. Amebas, tapeworms, and other parasites may create cerebellar cysts or masses.
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Vascular Disorders$^{5,29,30,64-68}$

Ischemic disease and hemorrhage in the posterior fossa seldom give rise to cerebellar signs alone. Cerebellar deficits are usually accompanied by brainstem and cranial nerve findings, including nausea, vomiting, vertigo, and visual disturbances, which may dominate the clinical picture.

Cerebellar hemorrhage is estimated to account for about 10% of all intracranial hemorrhages and a few percent of all strokes (Fig. 19–8). Cerebellar hemorrhage typically manifests as an acute onset of headache, repeated vomiting, vertigo and dizziness, and an inability to walk or stand.$^{64,65}$ Coma develops over hours or days in about 50% of these patients. In many cases, cerebellar hemorrhage is not suspected until neuroimaging or autopsy. The typical patient is hypertensive and older than 60 years of age, and frequently has a prior history of transient neurologic symptoms.

Although cerebellar infarction is more common than cerebellar hemorrhage, it represents only about 1% of all strokes (see Chapter 21).$^{66-68}$ Infarction in this region, however, has one of the highest mortality rates, estimated to be 20% to 50%. Diagnosis is often missed because of the wide range of clinical presentations. Actually, many patients have few cerebellar signs, despite radiologic evidence of cerebellar infarction. New imaging techniques have greatly increased the accuracy of diagnosis and suggest that its incidence is greater than heretofore suspected. The cerebellum is supplied by distal branches of the posterior inferior cerebellar artery, the anterior inferior cerebellar artery, and the superior cerebellar artery, all of which are supplied by the basilar artery. Although cerebellar infarction usually involves multiple vessels, occlusion of any one of the three principal arteries supplying the

Figure 19–8. Large hemorrhage (hematoma) of the cerebellum. From Hirano, A (ed): Color Atlas of Pathology of the Nervous System, ed 2. Igaku-Shoin, Tokyo, 1988, p 69, with permission.)
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cerebellum may give rise to specific signs and symptoms. Many different clinical patterns may develop, but unsteadiness of gait, dizziness, nausea, and vomiting are common early symptoms. Cerebellar infarction with edema formation can lead to sudden respiratory arrest due to increased intracranial pressure in the posterior fossa.

Intoxications

Cerebellar dysfunction may occur in association with exposure to a wide variety of toxins, including drugs, solvents, and heavy metals. These toxins may adversely affect the cerebellum directly or as part of a more generalized encephalopathy.

Practically all drugs given at high enough doses can cause neurologic signs and symptoms, including those indicating cerebellar dysfunction. The drug-induced cerebellar syndrome is characterized by transient gait ataxia, dysarthria, and nystagmus. Symptoms usually subside with discontinuation of the offending agent. The most common form of this syndrome is that associated with anticonvulsant medications. Certain cardiac agents, antineoplastic agents, and lithium may produce similar findings.

Recreational or accidental exposure to a wide variety of volatile solvents may cause ataxia along with other neurologic problems, including psychoses, cognitive impairment, and pyramidal signs. As with drug toxicity, these deficits are usually reversible unless exposure has been heavy and prolonged. These volatile chemicals are ubiquitous in our society and are found in many products, such as adhesives, solvents, aerosols, and fire extinguishers. Unfortunately, they are increasingly a choice for recreational abuse, with devastating neurologic consequences.

Poisoning with heavy metals such as mercury, manganese, bismuth, thallium, and lead can also result in neurologic syndromes, including prominent ataxia.

Injury Due to Physical or Mechanical Trauma

Direct mechanical trauma to the head, particularly in the area of the occiput, can produce cerebellar hemorrhage and tissue disruption (see Chapter 20). In most physical trauma resulting in closed-head injury, however, cerebellar dysfunction is not particularly apparent clinically and is overshadowed by the sequelae of the rest of the central nervous system damage. As some patients emerge from the acute phase of closed-head injury, cerebellar deficits may become more prominent.

The cerebellum has one of the highest rates of oxygen consumption in the nervous system and is particularly sensitive to oxygen deprivation. Following severe brain hypoxia, however, signs of cerebellar dysfunction may be overshadowed by diffuse cerebral dysfunction. The cerebellum is also particularly sensitive to thermal injury. Cerebellar dysfunction is known to occur following hyperthermia, whether it is due to heat stroke or prolonged fever. Radiation-induced injury to the cerebellum can result from both therapeutic and accidental exposure to ionizing radiation, manifested as diffuse atrophy and various functional deficits.

Metabolic Disorders

A number of inherited and acquired metabolic disorders are associated with cerebellar dysfunction. Disorders of lipids, the urea cycle, pyruvate and lactate metabolism, and some aminoacidurias are associated with cerebellar symptoms. Some of these disorders manifest in infancy or early childhood; others are not evident until later in life. They vary markedly in their severity and the extent to which they are progressive. Genetically determined metabolic disorders may give rise to either intermittent bouts of ataxia, due to the accumulation of circulating neurotoxic substances such as ammonia, or to persistent progressive ataxia. These metabolic disorders often cause disordered function at
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multiple sites in the nervous system. Accordingly, affected patients may present, in addition to cerebellar signs and symptoms, additional symptoms such as vomiting, headache, involuntary movements, seizures, confusion, and varying degrees of mental retardation.

Acquired disturbances of liver function, electrolyte balance (e.g., hyponatremia), and endocrine activity may also produce cerebellar findings. For example, hypothyroidism may be associated with an ataxic syndrome in both children and adults, as well as an accompanying peripheral neuropathy described in Chapter 15.

Demyelinating and Dysmyelinating Disorders

Many of the nerve fibers of both the peripheral and central nervous systems are myelinated and depend on this myelin for normal impulse propagation. Myelin is disturbed in a variety of disorders, both acquired and inherited, with resultant abnormalities in both the speed and the quality of impulse conduction (see Chapter 22). In some of these disorders, normal myelin may be damaged or destroyed (demyelinating diseases). In others, myelin is never properly formed (dysmyelinating diseases). Both the spinocerebellar pathways and the cerebellum contain abundant myelin and may be damaged by these types of disorders.

The most common of the demyelinating diseases of the CNS is multiple sclerosis (see Chapter 22), which is characterized by multisystem demyelination and clinical features encompassing spasticity, visual and oculomotor disturbances, urinary dysfunction, and cerebellar deficits. The classic signs of cerebellar dysfunction are common in multiple sclerosis in a variety of combinations, which may include dysarthria, instability of head and trunk, intention tremor, and inco-ordination of voluntary movements and gait. Cerebellar signs such as nystagmus and ataxia may appear early in the disease. Although most patients with multiple sclerosis have clinical manifestations referable to damage to many areas of the nervous system, in a few patients, cerebellar deficits predominate throughout much of the course of the disease. The cerebellar deficits may be severe and may make a significant contribution to patient disability.

Cerebellar dysfunction may result from the direct involvement of the cerebellum or may be due to involvement of spinocerebellar tracts. Demyelinating lesions (plaques) may be found randomly distributed throughout the cerebellar hemispheres, the peduncles, in the vicinity of the dentate nuclei, and in the spinocerebellar tracts.

Certain dysmyelinating diseases are also associated with progressive cerebellar dysfunction. Although cerebellar deficits are not a predominant component of the leukodystrophies, pathologic examination often reveals areas of demyelination throughout the cerebellar system, as well as in the cerebrum.

RECOMMENDED READINGS


Disorders of Central Motor Control