THE neural components required for the execution of smooth volitional and reflex movements are complex. The relationship of self to surroundings in space is necessary and requires the integration of visual, vestibular, and proprioceptive sensory information. Precise coordination of agonist and antagonist muscles, with feedback modulation of force and excursion, is required to execute the adroit movements of eyes, trunk, and limbs, which are part of everyday experience. A complicated, phylogenetically ancient system oversees these operations. Disorders of this system, resulting in the loss of coordination of volitional and postural movements, is known as ataxia (Greek ataktos, out of order).

Although encompassing an array of congenital and acquired structural and metabolic disorders, childhood ataxia is an approachable clinical problem. The history and physical examination, coupled with appropriate imaging studies and other laboratory tests, usually directly lead to an appropriate diagnosis. Many of these disorders are treatable; however, other disorders carry significant risks of genetic recurrence, which must be recognized by the physician so that appropriate counseling for patients and families can be provided.

NEUROANATOMY, PHYSIOLOGY, AND EMBRYOLOGY

At the center of this modulating system controlling coordination of movement and posture is the cerebellum, a division of the embryonic metencephalon. During the development of the nervous system, the cerebellum arises from paired thickenings of the neural tube's dorsal alar plate and the rhombic lips, which appear by 8 weeks of gestation. Neuroblasts from this region will proliferate and migrate to form the cerebellar cortex and its deep nuclei. Posterior midline fusion occurs in the third month, resulting in a thickened plate, with a dorsal marginal layer, central mantle layer, and ventral neuroepithelial layer. The basic cerebellar structure overlying the fourth ventricle, pons, and medulla is complete by 3 months and has achieved much of its postnatal appearance by 8 months' gestation, with the fissures and lobules of the midline vermis developing 1 to 2 months before those of the cerebellar hemispheres. Neuroblasts from the nascent neuroepithelial layer of the cerebellar plate migrate outward to the marginal layer surface of the embryonic cerebellum and form a proliferative zone known as the external granular layer. In the sixth month of development, cells from this external granular layer begin to migrate inward toward differentiating Purkinje cells derived
The trilaminar cerebellar cortex receives its input via mossy fibers (from the vestibular nuclei, spinal cord, brain stem, and cerebrum) and climbing fibers (from inferior olives). The mossy fibers synapse in the glomeruli with excitatory granule cells (which activate the Purkinje cells) and with Golgi cells, which inhibit mossy fiber input to neighboring glomeruli. The granule cell axons synapse in the molecular layer with inhibitory basket cells and outer stellate cells, which in turn inhibit the activity of neighboring granule cell axons. The climbing fibers branch in the white matter to reach the molecular layer, where they excite Purkinje cells and produce a strong surrounding inhibition of neighboring Purkinje cells through the basket cells and outer stellate cells. The net effect of mossy fiber and climbing fiber activation is to produce activation of a group of Purkinje cells, with a sharply contrasting zone of inhibition surrounding the activated center. The Purkinje cell output is inhibitory and projects to the deep cerebellar nuclei.

from the deeper mantle layer. Depending on where they come to lie, the external granular layer cells give rise sequentially to the granule cells, the basket cells, and the stellate cells found in the mature cerebellum. The cerebellar cortex, then, consists of an outermost molecular layer with stellate and basket cells, an intermediate Purkinje cell layer, and a deep granular layer with granule and inner stellate (Golgi) cells. The neurons of the four pairs of deep cerebellar nuclei, the fastigial, emboliform, globose, and dentate nuclei, are derived from the embryonic mantle layer. Cell migration and synaptogenesis in the cerebellum continue throughout the first year and a half of postnatal life.

Much is known about the intercellular relationships and cellular physiology of the mature cerebellum, where neurons are arrayed in almost crystalline regularity (see Figure 17.1). Afferent fibers arrive in the cerebellum either as climbing fibers from the contralateral inferior olivary nucleus of the medulla or as mossy fibers from contralateral pontine nuclei as well as both ipsilateral and contralateral spinal and lower
brain stem nuclei. The mossy fibers terminate within glomeruli of glial cells in the granular layer, forming excitatory synapses with granule cells and Golgi cells. The granule cells send axons to the molecular layer where they form excitatory synapses with longitudinal rows of Purkinje cells. These long axons synapse with parallel rows of outer stellate and basket cells, which function as inhibitory interneurons to "turn off" the Purkinje cells in rows adjacent to those excited by the granule cell's input. The Golgi cells excited by the mossy fibers also act as inhibitory interneurons within the glomeruli, decreasing the response of granule cells to subsequent mossy fiber inputs and sharpening the border between excited and inhibited Purkinje cells in the cortex.

Climbing fibers divide in the cerebellar white matter, traveling directly to widespread but related areas in the Purkinje cell layer where they function similarly to granule cells, producing an excitatory effect on a group of Purkinje cells and have an especially strong inhibitory effect on surrounding Purkinje cells via the outer stellate and basket cells. Some evidence suggests that the climbing fibers can be involved in motor learning within the cerebellum. All cerebellar cortical output is conducted through the axons of the Purkinje cells, whose rhythmic output is inhibitory on their targets and whose projections run to the deep cerebellar nuclei and the vestibular nuclei of the brain stem.

The cerebellum is traditionally divided from three major anatomic regions based on ontogeny and relative phylogenetic similarities (see Figure 17.2). The most evolutionarily conserved region of the cerebellum is the archicerebellum, consisting of the flocculonodular lobe, the lingula, and a portion of the uvula. The second subdivision is the paleocerebellum, consisting of the midline uvula, pyramis, and posterior vermis. The third and most recent subdivision is the neocerebellum, consisting of the large cerebellar hemispheres and the middle portion of the vermis.

A more clinically useful categorization of the cerebellum based on regional function has been developed. These three subdivisions include the vestibulocerebellum (controlling balance and eye movements); the spinocerebellum (controlling trunk and limb movements); and the cerebrocerebellum (modulating planning and execution of

**Figure 17.2** Anatomic subdivisions of the cerebellum: The cerebellum is divided into three regions based on either phylogenetic (shown in the figure) or functional criteria. The archicerebellum corresponds to the vestibulocerebellum; the paleocerebellum and medial part of the cerebellar hemispheres make up the spinocerebellum; and the remainder of the neocerebellum corresponds to the cerebrocerebellum.
The vestibulocerebellum receives input from the vestibular labyrinth directly and from neurons in the vestibular nuclei. Their axons pass through the inferior cerebellar peduncle (restiform body) and are projected to the flocculonodular lobe and portions of the vermis. These regions of cerebellar cortex in turn project Purkinje cell axons to the fastigial nucleus and then directly back to the vestibular nucleus in the brain stem via the inferior cerebellar peduncle. Disorders of the vestibulocerebellum result in gait ataxia, vertigo, truncal unsteadiness, and nystagmus.

The spinocerebellum receives input from two major pathways: the dorsal spinocerebellar tract and the ventral spinocerebellar tract. The dorsal spinocerebellar tract receives proprioceptive and cutaneous sensory information from muscle spindle afferents, Golgi tendon organs, and cutaneous receptors. The tract arises in the dorsal spinal cord for the lower extremities and in the cuneate nucleus of the medulla for upper extremities, sending projections ipsilaterally to the cerebellar cortex via the inferior cerebellar peduncle. Most of these fibers project somatotopically to the vermis and medial regions of the cerebellar hemispheres.

The ventral spinocerebellar tract receives information about the activity of inter-
neurons in the gray matter of spinal cord motor centers involved in movements of the arms and legs. Axons of neurons in this tract representing the lower extremities decussate at their spinal cord level and ascend in the contralateral ventral part of the cord, crossing again in the brain stem and thereby functioning ipsilaterally to send their axons through the superior cerebellar peduncle (brachium conjunctivum). Axons of neurons in the tract representing the upper extremities (the rostral spino cerebellar tract) ascend without crossing and enter their ipsilateral superior cerebellar peduncle. The ventral and rostral spino cerebellar tracts terminate somatotopically in the same regions of cerebellar cortex as those of the dorsal spino cerebellar tract. Purkinje cells in these regions project back to their ipsilateral fastigial, globose, and emboliform deep nuclei, which in turn send axons to the ipsilateral vestibular nuclei and brain stem via the inferior cerebellar peduncle and to the contralateral red nucleus in the midbrain via the superior cerebellar peduncle. Descending pathways, such as the corticospinal tract, rubrospinal tract, and reticulospinal tract, exert significant modulatory effects on the activity of the spino cerebellum. Disorders of the spino cerebellum produce a wide-based gait, gait ataxia, hypotonia, tremor of the head and trunk (titubation), and coarse incoordination of large-amplitude arm and leg movements.

Afferent pathways to the cerebro cerebellum arise in the brain stem, which has in turn received input from the ipsilateral cerebral cortex. Neurons in the pons and in the brain stem reticular formation send their axons through the contralateral middle cerebellar peduncle (brachium pontis) to the cortex of the cerebellar hemisphere. The Purkinje cells send their axons to the dentate nucleus, which, in turn, send its projections through the contralateral superior cerebellar peduncle to the ventral lateral nucleus of the thalamus and directly to the cerebral cortex. Dysfunction of the cerebro cerebellum results in clumsy gait with a tendency to fall toward the affected cerebellar hemisphere, hypotonia, dysmetria, intention tremor, impaired check and rebound, difficulty with rapid alternating movements, and nystagmus.

Clinical Syndromes of Ataxia

Any component of the movement and coordination systems can be affected by injury, illness, or genetic diseases. Improper vestibular, visual, somatosensory, and proprioceptive input, defective cerebellar processing of sensorimotor data, and difficulty with planning or executing movement before and after proper cerebellar processing can all lead to a breakdown in the execution of volitional and postural movements (see Table 17.1). The term "ataxia" is used clinically for deficits of cerebellar proprioceptive input and defects of cerebellar processing. Most patients with ataxia can be assigned to one or more of three basic ataxic syndromes: sensory ataxia, the midline cerebellar syndrome, and the lateral cerebellar syndrome. Each of these syndromes in turn suggests certain diagnoses and thus specifies a particular approach to diagnostic laboratory and neuroimaging studies.

Sensory ataxia is a term applied to a disturbance of gait and limb movements that results from the loss of proprioceptive input. Typical diseases producing damage to the posterior columns of the spinal cord include tertiary lues (tabes dorsalis) and vitamin B₁₂ deficiency (subacute combined degeneration), which are now relatively uncommon. In children, injuries to the spinal cord, tumors, and genetic diseases, as well as peripheral sensory neuropathy, can also produce sensory ataxia. Children with sensory ataxia are unsteady on their feet and frequently fall. They have a broad-based, unsteady gait and occasionally, there is a "slapping" quality of their walking. Stretch reflexes are absent. Patients can improve their stability by relying heavily on visual cues to maintain
Table 17.1 Problems of Noncerebellar Coordination

<table>
<thead>
<tr>
<th>PROBLEMS OF INPUT</th>
<th>PROBLEMS OF OUTPUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestibular dysfunction</td>
<td>Movement disorders</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Tremor</td>
</tr>
<tr>
<td>Toxins</td>
<td>Choreoathetosis</td>
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<tr>
<td>Visual perceptual deficits</td>
<td>Myoclonus</td>
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<tr>
<td>Somatosensory deficits</td>
<td>Paralysis</td>
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<td>Ideomotor apraxia</td>
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</table>

The cerebellum receives information from diverse somatic and special sensory pathways. Cerebellar output modulates complex motor activity arising in the cerebral cortex, basal ganglia, and brain stem. Problems in any of these systems can lead to incoordination of balance and movement. Defects with cerebellar processing of this sensory and motor information are properly termed "cerebellar ataxia."

their balance. Standing erect with the feet close together and eyes closed usually results in falling to one side or the other (positive Romberg sign). Nystagmus and titubation are absent.

The signs and symptoms of a midline cerebellar syndrome are symmetric and result from dysfunction of the vestibulocerebellum and medial spinocerebellum; the hallmarks are nystagmus and gait ataxia. Nystagmus is a rhythmic conjugate oscillation of extraocular movement with a slow drift component and a fast, opposing jerk component (see Chapter 13). In the midline cerebellar syndrome, gaze-evoked (gaze paretic) nystagmus is seen and is characterized by inability to maintain deviation of the eyes away from the center, nystagmus with the slow component toward the midline and worsened by lateral deviation of the eyes, lack of fatigability, and constant frequency. Occasionally, an unusual form of nystagmus (rebound nystagmus) can be observed in which deviation of gaze to the side produces typical gaze-evoked nystagmus, which after 20 to 30 seconds decreases in amplitude and then returns with the fast component in the opposite direction from that originally seen. This form of nystagmus is specific for cerebellar pathology. The ataxic gait observed in midline cerebellar syndrome is characterized by a wide-based stance (even in toddlers the feet are normally not spaced wider apart than the shoulders), irregular halting steps, and a truncal tremor or wavering. Closing the eyes usually does not dramatically worsen the instability. Other signs of this syndrome are head titubation, which can be rocking or rotatory, a head tilt or turn, and ocular dysmetria, in which there is "overshoot" of volitional movements.

The lateral cerebellar syndrome is manifested ipsilateral to the involved hemisphere(s) and results from dysfunction of the cerebrolateral cerebellum and lateral spinocerebellum. The cardinal features of this syndrome include limb ataxia, dysarthria, and hypotonia. Limb ataxia is manifested by a side-to-side kinetic or intention tremor elicited by reaching for objects, dysmetria (both side-to-side wavering and past-pointing on finger-nose-finger and heel-knee-shin testing), and the loss of the ability to modulate limb movements once started (impaired check and rebound). Dysarthria is characterized by a slow, slurred speech that can have a scanning quality. Hypotonia and pendular tendon stretch reflexes reflect a loss of tonic cerebellar input to spinal motor
| Table 17.2 Cerebellar Ataxias Classified by Disease Course and Associated Neurologic Findings |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
| **Acute**                                  | **Chronic Progressive**                      | **Chronic Nonprogressive**                   | **Intermittent**                            |
| "Pure"                                     | "Pure"                                      | "Pure"                                      | "Pure"                                     |
| Postviral                                   | Ataxia-telangiectasia                       | Cystic malformations                        | Toxins                                     |
| Infestations                                | Tumors                                      | Dandy-Walker syndrome                       | Aminoacidopathies                           |
| Viral                                       | Toxins                                      | Cerebellar malformations                     | Familial paroxysmal                         |
| Bacterial                                   |                                             | Residual postviral                           | Postconvulsive                              |
| Other                                       |                                             | Residual after hyperthermia                  | Mevalonic aciduria                          |
| Migraine                                    |                                             | Residual after toxins                        |                                            |
| Stroke                                      |                                             |                                              |                                            |
| Hyperthermia                                |                                             |                                              |                                            |
| Toxins                                      |                                              |                                              |                                            |
| + Neuropathy                                | + Neuropathy                                | + Neuropathy                                | + Neuropathy                                |
| Toxins                                      | Friedreich ataxia                           | Residual after toxins                        |                                            |
| Guillain-Barré syndrome                     | Refsum (HMSN IV)                            |                                              |                                            |
|                                             | Metachromatic leukodystrophy                 |                                              |                                            |
|                                             | Spino-cerebellar degenerations              |                                              |                                            |
| + ICP                                       | + ICP                                       | + ICP                                       |                                            |
| Hydrocephalus                               | Tumors                                      | Cystic malformations                        | Hydrocephalus                               |
| Hemorrhage                                  | Hydrocephalus                               | Chiari malformations                        | Toxins                                     |
| Tumors                                      | Toxins (lead)                               |                                              |                                            |
| Toxins (lead)                               |                                              |                                              |                                            |
| + CNS                                       | + CNS                                       | + CNS                                       | + CNS                                       |
| ADEM                                        | OPCAs                                       | Malformations                               | Migraine                                    |
| Infections                                  | Mitochondrial diseases                      | Static encephalopathy                       | Aminoacidopathies                           |
| Migraine                                    | Inborn errors of metabolism                 | "Ataxic cerebral palsy"                     | Biotinidase deficiency                      |
|                                             | Storage diseases                            |                                              |                                            |
|                                             | Neuronal ceroid lipofuscinosis              |                                              |                                            |
|                                             | Niemann-Pick type C                         |                                              |                                            |
|                                             | Other                                       |                                              |                                            |
| + Opsomyoclonus                             | + Opsomyoclonus                             | + Opsomyoclonus                             | + Opsomyoclonus                             |
| Neuroblastoma                               | Neuroblastoma                               | Residual after neuroblastoma                | Neuroblastoma                               |
| Toxins (tin, DDT)                           | Progressive myoclonic ataxias               |                                              |                                            |
|                                             | Pelizaeus-Merzbacher disease                |                                              |                                            |

ADEM, acute disseminated encephalomyelitis; ICP, intracranial pressure; HMSN, hereditary sensorimotor neuropathy; OPCA, olivopontocerebellar atrophy.
centers. Other features seen in the lateral cerebellar syndrome are oculomotor dis-orders, including nystagmus, ocular dysmetria, impairment of rapid alternating move-ments (adiadokokinesia), and dysgraphia.

The features of these three syndromes are commonly intermixed, but the clinician is usually able to localize the source of the patient's symptoms and direct further evaluation. Generally, sensory ataxia directs one's attention to the peripheral nerves and spinal cord, and the lateral cerebellar syndrome, especially if asymmetric, suggests a focal cerebellar lesion. The midline cerebellar syndrome can be due to a wide variety of structural and metabolic causes. The toxic, metabolic, and hereditary ataxias are usually symmetric and can evoke symptoms referable to each or all of the ataxia syndromes listed, while structural lesions often present with asymmetric findings (see Table 17.2).

Table 17.2 presents a classification of cerebellar ataxias by disease course and associated neurologic findings. Cerebellar ataxias are classified first by the course of the illness: acute, chronic and progressive, chronic and nonprogressive, or intermittent. Associated neurologic features are then sought (ataxia alone, as a "pure" finding, with peripheral neuropathy, with signs of increased intracranial pressure, with other CNS signs, or with opsoclonus and myoclonus). Several diagnostic possibilities are then suggested in each category. Note that acute ataxia usually does not suggest heredo-degenerative or genetic metabolic etiologies.

**CEREBELLAR MALFORMATIONS**

Isolated malformations of the cerebellum are uncommon and usually do not present with clear signs of cerebellar ataxia. Rather, anomalies are often a part of a more widespread dysgenesis of the nervous system, and other signs of neurologic dysfunction, including hypotonia, developmental delay, and hydrocephalus, reflect this fact. An important consideration in the assessment of cerebellar structural abnormalities is the differentiation between cerebellar atrophy and cerebellar malformation. High-resolution magnetic resonance imaging (MRI) can be of great value in differentiating between atrophy in which a normally formed cerebellum is shrunken and malformation in which the proper orientation and number of folia of the vermis and hemispheres have not developed (see Table 17.3).

The entire cerebellum can be small and hypoplastic as an isolated familial trait or as a part of Down syndrome (trisomy 21), trisomy 18, and trisomy 13. A number of toxic and infectious exposures in utero can also lead to a globally small cerebellum but usually cause more widespread injury, resulting in developmental delay and microcephaly.

Posterior fossa cystic malformations that affect the cerebellum include the Dandy-Walker syndrome, the Dandy-Walker variant, and the mega cisterna magna. Generally, these anomalies represent a continuum of structural abnormalities, although their etiologies can be quite different. The typical Dandy-Walker malformation results from failed midline fusion of the dorsal rhombic lips in the embryo. The fourth ventricle is greatly dilated and fills most of the posterior fossa, which also is enlarged, producing a shelflike occiput on physical examination. The tentorium cerebelli is displaced upward and the cerebellar vermis is absent or severely hypoplastic, with small cerebellar hemispheres splayed anterolaterally by the dilated fourth ventricle. The Dandy-Walker variant shows a similar dysgenetic cerebellar vermis and hemispheres, but the tentorium is normal to low in its location, and the fourth ventricle is of normal size. The space between the small cerebellar hemispheres is filled with cerebrospinal fluid (CSF) that
**Table 17.3 Some Ataxias Grouped by Age of Onset**

| Infants (Birth–23 mo) | Malformations  
| --- | ---  
| | Cystic malformations (Dandy-Walker syndrome, mega cisterna magna)  
| | Hypoxic-ischemic injury  
| Genetic and metabolic diseases  
| | Leigh disease  
| | Mitochondrial diseases  
| | Metachromatic leukodystrophy  
| | Pelizaeus-Merzbacher disease  
| | Krabbe disease  
| Preschool Children (2–5 yr) | Postviral infection  
| | Acute cerebellar ataxia  
| | Guillain-Barré syndrome  
| | Acute disseminated encephalomyelitis (ADEM)  
| | Varicella-associated ataxia  
| Toxins  
| Tumor  
| Paraneoplastic (occult neuroblastoma)  
| Trauma  
| | Posterior fossa subdural or epidural hemorrhage  
| | Postconcussion syndrome  
| Infections  
| | Viral encephalitis  
| | Cerebellar abscess  
| Migraine  
| Genetic and metabolic diseases  
| | Ataxia-telangiectasia  
| | Progressive myoclonic ataxies  
| | Late infantile and juvenile neuronal ceroid lipofuscinosi s  
| | Biotinidase deficiency  
| | Niemann-Pick disease, type C  
| | Autosomal dominant cerebellar ataxias  
| | Olivopontocerebellar atrophy (OPCA)  
| | Friedreich ataxia  
| | Mitochondrial diseases  
| | Lactic acidoses  
| School-age Children (6–12 yr) | (Many of the disorders of preschool children occur in this age group.)  
| | Paraneoplastic (Hodgkin lymphoma)  
| | Postradiation  
| Genetic and metabolic diseases  
| | Lafora body disease  
| | Juvenile Tay-Sachs disease  
| | X-linked adrenal leukodystrophy  
| | Hartnup disease  
| | Wilson disease  
| | Abetalipoproteinemia  
| | Mevalonate kinase deficiency  
| | Juvenile multiple sclerosis  
| Adolescents (13–18 yr) | (Many of the disorders of school-age children occur in this group.)  
| | Toxins  
| | Guillain-Barré syndrome (Miller-Fisher variant)  
| Genetic and metabolic diseases  
| | Olivopontocerebellar degeneration  
| | Heritable spinocerebellar ataxias  
| | Niemann-Pick disease, type C  
| | Mannosidosis type II  

*A number of common etiologies and specific entities are listed for varying ages of onset. Many of these disorders include ataxia as part of more widespread nervous system dysfunction. Genetic and metabolic disorders can present at any age; although the spectrum of diseases to consider is influenced by the*
communicates with the cisterna magna. The mega cisterna magna is characterized by an intact cerebellar vermis and fourth ventricle but an enlarged posterior fossa. All three of these anomalies can present with manifestations of developmental delay, hypotonia, or hydrocephalus. The prognosis and severity of developmental delay are related to the extent of associated supratentorial malformations, which include complete or partial agenesis of the corpus callosum, heterotopias, and polymicrogyria.

Joubert syndrome is characterized by aplasia of the cerebellar vermis, a “bat-wing” cross-sectional shape of the fourth ventricle, malformations of the deep cerebellar nuclei, and abnormalities of the lower brain stem. The syndrome is manifested by episodic hyperpnea in infancy, oculomotor abnormalities, developmental delay, and ataxia. It is inherited as an autosomal recessive trait.

Chiari malformations are complex developmental anomalies of posterior fossa structures, including the cerebellum. They range from an extension of the cerebellar tonsils through the foramen magnum (Chiari Type I) to cerebellar tonsillar extension through the foramen magnum with associated kinking of the brain stem, “beaking” of the midbrain tectum, a small fourth ventricle, and a small posterior fossa (Chiari Type II). The aqueduct of Sylvius can be abnormally divided into smaller channels, resulting in hydrocephalus, because of inadequate egress of the CSF. The rare Chiari Type III is the combination of Chiari Type II malformation with anoccipital encephalocele. The Chiari Type I anomaly can present in childhood or adult life with compression of the cervicomедullary junction with signs and symptoms of cervical cord syringomyelia. These signs and symptoms are sometimes initially apparent following trauma to the neck, such as in the case of an automobile accident. The Chiari Type II malformation is almost invariably associated with lumbosacral myelomeningocoele. Patients usually develop hydrocephalus, which requires ventricular shunting after closure of the spinal defect, and associated supratentorial malformations of the corpus callosum and cerebrum are not uncommon. When present, these supratentorial malformations increase the risk for subsequent developmental delay and retardation. MRI is particularly valuable, showing in sagittal planes the extent of these anomalies.

Platybasia is a descriptive term applied to flattening and upward displacement of the base of the skull, producing the appearance of a short neck and low posterior hairline on physical examination. Platybasia can occur as an isolated autosomal dominant trait or can be associated with bony malformations of the cervical spine and craniovertebral junction such as the Klippel-Feil anomaly, cystic posterior fossa malformations, and Chiari malformations. High cervical cord and lower brain stem compression as well as syringomyelia and syringobulbia can result. Lateral skull films and computed tomography (CT) of the basilar aspects of the skull readily show the defect(s), and surgical decompression of the occiput can sometimes relieve the symptoms.

TUMORS, VASCULAR LESIONS, AND TRAUMATIC INJURY

Primary central nervous system (CNS) neoplasms of the posterior fossa are common in childhood and rank only second to leukemia as a childhood cancer (see Chapter 8). In infants less than 2 years of age, the majority of brain tumors are supratentorial as they are in the adult population; however, in older children, more than 60% of brain tumors lie in the posterior fossa. These lesions present with a combination of various signs and symptoms of cerebellar dysfunction and secondary hydrocephalus from obstruction of the fourth ventricle. Symptoms of hydrocephalus include lethargy, vomiting, headache, and diplopia. Physical signs of hydrocephalus can include altered mental status, limi-
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...tion of vertical gaze (Parinaud syndrome), third and sixth nerve palsies, truncal ataxia, nuchal rigidity, and spasticity with hyperreflexia, especially in the adductors of the thighs. Papilledema is sometimes not apparent. In small children whose skull sutures have not yet fused, the fontanelle can bulge and the head can progressively enlarge. The tumor can present with signs of either the midline or lateral cerebellar syndrome, and any child with an asymmetric lateral cerebellar syndrome should raise the suspicion of a cerebellar tumor. The juvenile pilocytic astrocytoma (JPA) frequently arises in one cerebellar hemisphere, whereas the medulloblastoma, or primitive neuroectodermal tumor (PNET), arises from the cerebellar vermis in the region of the fourth ventricle. The incidence of these two tumor types is about the same, and together they account for the majority of posterior fossa tumors in children. Less common tumors that arise in the cerebellum and brain stem in childhood include ependymomas, brain stem gliomas, dermoid and epidermoid tumors, and acoustic neuromas. Histiocytosis-X can also involve the skull and posterior fossa. Metastatic tumors from remote cancers also occur but are much less common than in adults.

**Arteriovenous malformations and hemangioblastomas** can occur in the cerebellum and result in ataxia. The progression of symptoms can be gradual as the lesion grows or sudden if hemorrhage should occur. The presence of cerebellar hemangioblastomas should prompt a careful ophthalmologic examination for retinal hemangioblastomas of von Hippel-Lindau disease (see Chapter 9).

**Subdural, epidural, and parenchymal hematomas** can occur in the posterior fossa secondary to trauma or coagulopathy. Subdural hematomas of the tentorium cerebelli and the posterior fossa can occur subsequent to skull molding during delivery. The presenting signs of any of these lesions are usually those of a progressive lateral cerebellar syndrome, hydrocephalus, and brain stem compression. These conditions usually constitute neurosurgical emergencies, although some small subdural hematomas in the posterior fossa have been managed conservatively with good outcome. Very close observation and monitoring are indicated in all affected patients. Because the X-ray attenuation of fresh blood can be similar to that of bone on routine studies, some small posterior fossa bleeds can be easily overlooked on CT head scan. When clinical suspicion is high, thin CT sections with appropriate windows or MRI should be performed.

Closed head trauma can produce a postconcussive syndrome without evidence of structural CNS injury. Ataxia in this syndrome is less common than are irritability, behavioral changes, headache, and vertigo. Postconcussive syndrome should be entertained as a diagnosis only after structural damage has been excluded by appropriate neuroimaging studies.

Cerebellar stroke is uncommon in children and should always prompt investigation for structural vascular lesions of the vertebrobasilar system, cyanotic congenital heart disease predisposing to emboli, and hemoglobinopathies or coagulopathies. Viral illnesses causing vasculitis, such as varicella-zoster, can also lead to stroke.

Prenatal and perinatal hypoxic-ischemic injury can produce an ataxic syndrome in conjunction with spasticity and, often, mental retardation. This static encephalopathy ("ataxic cerebral palsy") is of variable severity and has a non-progressive course, probably resulting from the susceptibility of the large Purkinje cells to anoxic injury

Ataxia can also occur as a form of basilar migraine (see Chapter 15). The ataxia, which is symmetric, is often recurrent and can be accompanied by vertigo, alternating hemiplegia, and visual disturbances. Headache is frequently absent during the atactic episode but can occur later. Vertebrobasilar migraine can occur at any age but is most commonly seen in adolescent females. A family history of migraine is a helpful clue to the diagnosis as well as an earlier history of recurring abdominal cramping or pains, "cyclic vomiting," motion sickness, or sleepwalking. The diagnosis is made after proper
exclusion of other pathologic states. Prophylactic daily treatment with cyproheptadine (Periactin), beta-blockers, or phenobarbital are usually effective as treatment methods.

**Infection and Parainfectious Ataxias**

The cerebellum can be affected by any bacterial, viral, fungal, or protozoal agent that can involve the CNS. Usually, clinical evidence of meningitis or encephalitis is not limited to symptoms and signs referable to the cerebellum, and the ataxia is a component of a more florid presentation or a sequela of bacterial meningitis. Localized infections, such as cerebellar abscess (fungal or bacterial) and posterior fossa subdural empyema, can produce lateral and midline cerebellar syndromes. Presence of a fungal abscess should raise the concern of immune deficiency, including acquired immunodeficiency syndrome (AIDS) (see Chapter 20). Infection with the dog parasitic tapeworm *Echinococcosis* can cause cystic lesions in the cerebrum and/or cerebellum, which are treated surgically as well as by administration of antihelminthic drugs. Viral infections are the most common infectious disorders affecting the cerebellum and causing ataxia. They are either primary infections of the cerebellum by the offending virus or occur as a parainfectious cerebellar ataxia, presumably by an immune-mediated process. In an encephalitic process, the CSF usually shows evidence of inflammation, with or without protein elevation and lymphocytic pleocytosis. Viruses that have been documented to cause encephalitis (cerebellitis) include herpes simplex, varicella-zoster, arboviruses, echoviruses, enteroviruses, poliomyelitis, cytomegalovirus, rabies, Japanese B virus, and human immunodeficiency virus (HIV). The availability of treatment for some of these infections, such as acyclovir for herpes infections, has increased the need to rapidly and accurately define the offending virus. In viral encephalitis, it is sometimes possible to recover the causative agent from cultures of the CSF. The yields of identifying the offending virus can be increased by also culturing respiratory and oral secretions, blood lymphocytes, urine, and stool. Cerebellar ataxia as a primary manifestation of pediatric CNS HIV infection is uncommon, and the ataxia that is sometimes seen is probably a consequence of combined neocortical disease, peripheral neuropathy, and direct cerebellar involvement. The ataxia is overshadowed by a progressive developmental regression and spasticity observed in these children.

In parainfectious cerebellar ataxia, a striking global cerebellar syndrome can develop during or shortly after infection with any of a number of viruses, including varicella-zoster, Epstein-Barr, measles, mumps, and rubella viruses, Coxsackie virus, echovirus, and influenza viruses. In general, the CSF is normal, although a mild pleocytosis can be present; the causative agent cannot be isolated from the CSF, and the prognosis is generally better than that for encephalitis. Acute cerebellar ataxia occurring in conjunction with varicella-zoster virus infection occurs in about 1 in 500 cases of clinical varicella infection. A rapidly progressive syndrome characterized by irritability, vomiting, nuchal rigidity, nystagmus, slurred speech, and ataxic gait usually begins within 10 days of the appearance of the skin rash, although it can occasionally precede the rash. The CT and MRI head scans can be entirely normal as well as the CSF. Recovery is usually complete within a matter of weeks.

The Miller-Fisher variant of Guillain-Barré syndrome, manifested by ophthalmoplegia and areflexia, can occur after viral infections or vaccination and is increasingly recognized in children, including infants. The outlook is generally favorable with supportive care, although on occasion plasmapheresis or immunoglobulin therapy is required.

A parainfectious cerebellar syndrome has also been reported secondary to *Mycoplasma* pneumoniae, diphtheria, typhoid fever, and scarlet fever. High fever alone can
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sometimes produce ataxia as well, presumably because of Purkinje cell vulnerability to injury at temperature above 41°C. Ataxia from hyperpyrexia usually resolves with defervescence, but rare examples of permanent cerebellar injury from notable hyperthermia can occur.

An acute cerebellar ataxia can develop in early childhood over a period of hours to days; commonly, there is preceding history of an antecedent nonspecific illness such as a gastroenteritis or an upper-respiratory infection. This syndrome is a common cause of cerebellar dysfunction generally occurring in children from 1 to 4 years of age; the precise pathophysiology remains unknown. Typically, the child wakes one morning with a truncal tremor and a wide-based gait, which progresses over the course of a day or so to severe truncal and limb ataxia; slurred and scanning speech and coarse, jerky involuntary tremors of the limbs and trunk are present and can persist at rest and appear to have a myoclonic quality. Gaze-evoked nystagmus is present in about one half of patients, and some develop chaotic conjugate movements of the eyes. Few other neurologic signs are present, and the child is afebrile. CT and/or MRI head scans are usually normal, although there is one report of a transient cerebellopontine demyelination documented at MRI. The CSF is usually normal, but in about one fourth of patients there is a mild lymphocytic pleocytosis of less than 30 cells/mm³. CSF protein level is normal at the onset but can increase slightly over the course of the illness. The diagnosis is made after excluding other causes of cerebellar dysfunction, such as tumor, intoxication, paraneoplastic syndrome, and infection. Neuroimaging (preferably MRI) and CSF examination are warranted in most instances.

In contrast to its rapid onset, the resolution of the acute cerebellar ataxia is commonly prolonged. Most patients recover gradually over several months, although some may recover in as little as several weeks. Intercurrent illnesses during recovery can cause temporary exacerbations of ataxia, with gradual recovery continuing when the illness ends. The persistence of symptoms for more than 6 months increases the risk of permanent neurologic sequelae. Children who initially demonstrate not only truncal and limb ataxia, but dysarthria, abnormal eye movements, hypotonia, or tremor have a higher risk of permanent neurologic sequelae. Generally, about one half of patients attain full recovery within 6 months of onset of illness, but about one third are ultimately left with significant neurologic sequelae, including ataxia, clumsiness, behavioral problems, speech and language delay, and mental retardation.

Patients can show symptomatic improvement with the administration of steroids, preferably adrenocorticotropic hormone (ACTH), although prednisone is sometimes of benefit. Unless the child is notably disabled by the ataxia for a relatively long time, the administration of steroids is usually not suggested because of the potentially serious side effects. Steroid therapy can be helpful in alleviating symptoms in children who fail to improve within 6 months, although those who are steroid-responsive may become steroid-dependent, with recrudescence of symptoms when steroid dosages are tapered. There is no evidence that treatment with steroids alters the ultimate outcome of the illness.

These postinfectious and parainfectious cerebellar syndromes must be distinguished from cerebellar involvement in the more widespread process of acute disseminated encephalomyelitis (ADEM). This postinfectious or postvaccinal demyelinating process can present in children as well as in adults, usually several weeks following a viral illness or vaccination, with multifocal neurologic signs and mental status changes. MRI and CT head scans show patchy subcortical white matter demyelination in the cerebral and cerebellar hemispheres; occasional lesions of the basal ganglia, brain stem, and spinal cord can be apparent. These lesions—unlike encephalitis—do not contrast-enhance and in the older adolescent must be differentiated from multiple
sclerosis. Recovery from ADEM is complete in about 90% of patients and is often hastened by the administration of steroids; about one third of patients have neurologic sequelae.

**Opsoclonus, Myoclonus-Ataxia Syndrome**

This uncommon triad of signs and symptoms, which can appear similar to the most severe forms of acute cerebellar ataxia in toddlers and preschool children, is important to recognize because it often heralds the presence of an occult neuroblastoma or ganglioneuroblastoma elsewhere in the body. There is symmetric truncal and limb ataxia, and a notable tremor can be present. Nystagnus can occur but is overshadowed by opsoclonus, which is characterized by involuntary irregular chaotic conjugate ocular movements, preventing ocular fixation. These rapid, intermittent ocular movements, sometimes described as “dancing eyes,” are dramatic in their appearance. Multifocal myoclonus is usually prominent but disappears in sleep. Opsoclonus, however, occurs when awake or asleep, and during sleep the rapid intermittent ocular oscillations are readily apparent under the closed eyelids.

There is usually an acute or subacute onset of signs and symptoms, which can occur over a matter of hours or days. Although it was once thought that opsoclonus was invariably present at some point in the illness, several well studied patients with the syndrome did not have opsoclonus. The neurologic syndrome can precede the detection of the occult tumor by months and, on occasion, as long as 2 years before tumor is detected. About 5% of children with neuroblastoma have the above-described syndrome, whereas about 65% of children with ataxia, myoclonus, and opsoclonus have occult neuroblastoma. Newer imaging techniques may increase the detection of small differentiated ganglioneuroblastomas, which have a tendency to spontaneously involute. The presence of the opsoclonus-myoclonus-ataxia syndrome confers a good prognosis for the neuroblastoma itself with an overall 2-year survival of 90% as compared with a 2-year survival of 30% for all patients with neuroblastomas; however, there is 50% risk of permanent neurologic sequelae even after the tumor has been removed.

The neuroblastoma can be found anywhere from the presacral region of the pelvis to the neck and is commonly found in the abdomen or posterior mediastinum. Metastatic bone marrow and spinal epidural lesions are common. Since the tumor is often small, testing of the urine for excess excretion of catecholamine metabolites (vanillylmandelic acid [VMA], 5-hydroxyindoleacetic acid [5-HIAA], metanephrines) is helpful only if results are positive, and the patient should have appropriate imaging studies completed. Sometimes a calcified mass can be seen on plain radiographs or CT of the chest and abdomen, but a small tumor can be easily missed. The most sensitive and specific test for occult neuroblastoma is a total body nuclear scan with radioactive I-131-metaiodobenzylguanidine (MIBG), a catecholamine precursor analog that is taken up by adrenergic and noradrenergic cells. An alternate approach is to perform a gadolinium-enhanced MRI scan of the pelvis, abdomen, chest, and neck. Unfortunately, few direct comparisons of the two methods are available. Normal imaging studies at initial presentation warrant repeat studies in the future. Treatment of neuroblastoma is complicated and yet evolving, but at this time the combination of surgery, radiation therapy, and chemotherapy is used, depending on the location, stage, and grade of the tumor.

The etiology of this syndrome is unknown, although it was initially thought that the tumor, derived from neural crest cells and often secreting catecholamines, was producing a neuroactive substance that caused the disorder. Evidence for this hypothesis is
lacking, and it is more likely that this syndrome is an immune-mediated paraneoplastic phenomenon. Correlations of the syndrome’s occurrence with markers of tumor biology, such as amplification of the c-myc oncogene and immune response to the tumor, are only now being studied.

Treatment with ACTH or prednisone can alleviate signs and symptoms, particularly the opsoclonus, in most patients. Unfortunately, reduction of the steroid dosage can lead to reappearance of the earlier signs and symptoms, and some patients require long-term steroid therapy with its potential adverse side effects.

**Toxins**

Many chemicals affect cerebellar function. Effects of various intoxications can be reversible or permanent. Many prescription and illicit drugs can cause ataxia (see Table 17.4). Anticonvulsant drugs, especially phenytoin and carbamazepine, but not valproic acid, can cause ataxia at therapeutic serum levels and are one of the most common causes of ataxia in a pediatric practice. Phenobarbital, primidone, and benzodiazepines can also cause ataxia when the serum levels are abnormally high, but the ataxia resolves when the serum drug levels are decreased. Polypharmacy can cause ataxia at lower serum drug levels than when one anticonvulsant drug is administered. Nystagmus is often prominent in these circumstances.

Ethanol intoxication causes prominent ataxia, dysarthria, and nystagmus. The ataxia is usually transient, but chronic alcoholism can produce a permanent midline cerebellar syndrome. This finding has been reported in adolescents as well as in adults. Other alcohols, such as methanol and ethylene glycol, also can cause ataxia.

Heavy metal poisoning by lead, mercury, and thallium also can cause ataxia. Lead encephalopathy in children presents with cerebral and cerebellar edema, and cerebellar dysfunction, as a false localizing sign, can be prominent. Mercury poisoning can result in ataxia accompanied by confusion, seizures, and tremor. Chronic thallium poisoning, while uncommon, is distinctive because of associated clinical features, including alopecia and evidence of central and peripheral nervous system injury.

Mushroom poisoning with *Amanita muscaria* can include ataxia as a part of a broader syndrome characterized by parasympathomimetic signs and symptoms.

There are some chemotherapeutic agents used in treatment of childhood cancers that can provoke ataxia as a side effect. Careful evaluation is needed to differentiate drug toxicity from CNS involvement by the cancer itself or from a paraneoplastic syndrome. Cytosine arabinoside (Ara-C) is a pyrimidine analog that inhibits deoxy-

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<th>TABLE 17.4 Drugs and Toxins as a Cause of Ataxia</th>
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<td><strong>ANTICONVULSANT DRUGS</strong></td>
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Ara-C, cytosine arabinoside; 5-FU, 5-fluorouracil; MESNA, sodium 2-mercaptothione sulfonate; DDT, dichlorodiphenyltrichloroethane.
ribo nucleic acid (DNA) polymerase when incorporated into replicating DNA. It is used in the treatment of lymphoma and leukemia and can be administered systemically or intrathecally. Intravenous administration produces CSF levels that are 40% of those in the plasma. The administration of high-dose Ara-C protocols in 1979 for relapsed leukemia and lymphoma and for nonlymphocytic leukemias led to the first reports of a variable but sometimes severe and irreversible cerebellar ataxia in 16% of treated patients who had received a cumulative Ara-C dose of at least 36 g/m².

5-Fluorouracil (5-FU) is a pyrimidine analog that inhibits thymidylate synthase and thus DNA replication. A dose-related reversible cerebellar syndrome can occur with its use in a variety of childhood cancers. Ataxia is seen in 10% of children treated with 20 mg/kg/week of 5-FU and is rare at doses below 15 mg/kg/week. When the drug is discontinued, ataxia resolves over a period of 1 to 2 months. Protocols using high-dose 5-FU have produced a high incidence of a more severe encephalopathy, including mental status changes in addition to ataxia.

Methotrexate, an inhibitor of dihydrofolate reductase and thus purine biosynthesis, is associated with a number of effects on the nervous system, including ataxia. Usually, the cerebellar signs are part of more widespread symptomatology. A syndrome of myelopathy, encephalopathy, seizures, and ataxias can occur days to weeks after the administration of intrathecal methotrexate. A more chronic form of methotrexate toxicity, typically seen months to years after a combination of intrathecal methotrexate and cranial irradiation, can include cerebellar sclerosis in addition to the more commonly seen leukoencephalopathy and cortical atrophy. The cerebellar pathology produces surprisingly few symptoms and presumably arises as a consequence of a widespread microangiopathy.

The combination of the alkylating agent ifosfamide and sodium 2-mercaptothane sulfate (MESNA; for prevention of hemorrhagic cystitis), used for treatment of many solid tumors, is associated with a high rate of reversible neurologic side effects. A global cerebellar syndrome is seen in up to 20% of patients during treatment and can be severe. It is usually accompanied by mental status changes. Its etiology is uncertain, but it can be due to a toxic metabolite of the ifosfamide. Impaired hepatic function and perhaps prior treatment with cisplatinum (CPDD) can predispose the patient to this reversible side effect. Procarbazine, used in the treatment of some CNS tumors, can also produce a dose-related cerebellar ataxia. Several chemotherapeutic agents can produce a sensory neuropathy that can lead to gait instability mimicking cerebellar ataxia.

**Genetic, Inherited Metabolic, and Degenerative Ataxias**

Only a few members of this diverse group of disorders present with ataxia alone, and even fewer present with the acute onset of ataxia, with a few notable exceptions. An extensive evaluation for genetic diseases and inborn errors of metabolism is usually not necessary for the patient presenting with an acute, relatively pure cerebellar syndrome. While the individual diseases in this group are uncommon, genetic ataxic disorders as a whole are not all that rare, and most pediatricians, neurologists, and internists will encounter these patients from time to time. Rather than attempting to commit detailed descriptions of rare diseases to memory, a practical systematic approach to diagnosis should be developed with reference information available for the particular disease.

The key to recognition and diagnosis of these disorders is to obtain a careful and complete history (see Chapter 1). Ataxia that is chronically progressive or intermittent should always suggest a genetic degenerative disease or an inborn error of metabolism as its cause. Metabolic and genetic ataxias are almost always symmetric and usually
preferentially involve midline cerebellar structures. The ataxia can be associated with other important neurologic findings. In this respect, it is useful to try to classify the ataxia as an isolated finding, part of a more widespread disorder of white matter with spasticity, peripheral neuropathy, or optic atrophy, or of a more widespread disorder of gray matter with developmental regression or dementia, seizures, retinal abnormalities and visual loss, movement disorders, or myoclonus. Some diseases present with evidence of both white and gray matter involvement, and many develop global involvement during the later stages.

Based on the history and physical examination, a differential diagnosis can be generated, and appropriate screening laboratory and neuroimaging studies can be performed; moreover, definitive studies can then be carried out to confirm the diagnosis.

An important consideration in any of these diseases is proper counseling of patients and families not only about the illness, possible treatment, and prognosis for the proband, but about the mode of genetic transmission and the prospective risk for recurrence. In many cases, issues of presymptomatic testing, carrier testing, and prenatal diagnosis will be raised, and the physician must be able to address the family’s concerns in this regard. In order to provide accurate and thoughtful advice in this rapidly expanding field, familiarity with the current medical literature is critical, and consultation with a qualified clinical geneticist is frequently necessary.

Several prototypic diseases exemplify this group of disorders. Friedreich ataxia is the typical spinocerebellar degeneration of childhood, transmitted as a recessive trait linked to DNA markers on chromosome 9q12-13. A milder “Acadian” form maps to the same chromosome site, and a similar phenotype can be transmitted as an autosomal dominant trait from a different genetic locus. While one of the most common hereditary ataxias, it is in fact rare, occurring in 1:100,000 persons. Heterozygotes are clinically normal. Neurologic symptoms can begin as early as age 2 years but usually come to medical attention around age 10 years, with progressive combined midline cerebellar and sensory ataxic syndrome, loss of proprioception, and areflexia. Romberg sign is often present. Vestibular involvement (50%) and delayed visual evoked potentials (65%) have also been described. Skeletal deformities are prominent and can be present at birth as the only sign of the disorder. A high arched foot (pes cavus) with hammer toes occurs in 75%, kyphoscoliosis in 80%, and cardiomyopathy with conduction defects in 50% to 90% of patients. Distal muscle wasting occurs as the disease progresses. Neuropathologic studies show a neuronal loss among the Purkinje cells and in Clarke’s column of the spinal cord. Progression is variable, and many patients experience prolonged “plateaus” of stable neurologic function. Cardiac disease and inanition from progressive weakness and incoordination account for early mortality.

Ataxia-telangiectasia (Louis-Bar disease) is a neurocutaneous disorder transmitted as a genetically heterogeneous autosomal recessive trait at a frequency of 1:40,000 persons (see Chapter 9). One common form maps to chromosome 11q23. The complete phenotype of this disorder is striking, with prominent progressive midline cerebellar ataxia and nystagmus, telangiectasias of the bulbar conjunctivae and skin, as well as oculomotor apraxia. Affected children can have a combined cellular and humoral immune deficiency, insulin-resistant hyperglycemia, and premature graying of the hair. A defect in repair of radiation-induced DNA damage appears to be the primary defect in this disease, and it is this problem that predisposes patients to lymphoreticular malignancies at a young age. Cultured fibroblasts from patients’ skin show a characteristic hypersensitivity to X-radiation. Serum alphafetoprotein is often elevated.

Ataxia can be a part of brain degenerative diseases such as neuronal ceroid lipofuscinosis (see Chapter 4). The late infantile form (Batten-Bielschowsky-Janssky disease, CNL2) is genetically distinct from the early infantile form (Santovouri disease,
CNLI, chromosome 1p) and the juvenile form (Spielmeyer-Vogt disease, CLN3, chromosome 16p12). In the late infantile form, a prominent ataxia is associated with corticospinal tract dysfunction, myoclonic seizures, developmental regression, pigmentary retinal degeneration, and dementia. In the juvenile form, the visual loss is striking with pigmentary retinopathy and associated with ataxia, corticospinal tract dysfunction, dementia, and seizures.

A large heterogeneous and confusing group of progressive ataxias, usually transmitted as an autosomal dominant trait, have been grouped under such headings as familial spino cerebellar ataxia, olivopontocerebellar atrophy (OPCA), the Ramsay-Hunt syndrome, Unverricht-Lundborg disease, familial spastic ataxia, and Marie-Holmes ataxia. These often imprecise and overlapping clinical classifications have made this diverse group of progressive neurodegenerative diseases difficult to readily understand. A simplified descriptive classification is gradually evolving.

Progressive myoclonic ataxia is a term applied to a group of disorders characterized by myoclonus and ataxia, with variable features of dementia, spasticity, and seizures, the latter leading to nosologic overlapping with the progressive myoclonic epilepsies, one of which maps to chromosome 21q22. These terms are preferable to previous eponymous terms. These disorders usually begin in childhood and are relentlessly progressive, tending to begin in affected family members at about the same age. The possibility of maternally transmitted mitochondrial diseases, such as myoclonus, epilepsy, with ragged red fibers (MERRF), must be considered.

One form of spino cerebellar ataxia, inherited as an autosomal dominant trait, with onset of signs and symptoms as early as young adulthood (SCA1) has been localized to chromosome 6p. Other dominant disorders with variable penetrance are characterized by ataxia and spasticity beginning in young adulthood or late adolescence. A family history of similar disease states and the combination of ataxia and spastic paraparesis usually suggest the diagnosis. The dominantly inherited OPCAs show evidence of progressive ataxia, dysarthria, tremor, cranial nerve dysfunction, and proprioceptive loss. Onset of the most common type, OPCA IV, can be seen in adolescence. A severe disease, OPCA III, can occur in the first year of life and is heralded by ataxia and visual loss with retinal pigmentary degeneration.

Patients with acute intermittent ataxia warrant special consideration. Aminoacidopathies, such as Hartnup disease and maple syrup urine disease, can present with episodic ataxia. Mevalonate kinase deficiency can present in a young child with episodic ataxia, hypotonia, and mevalonic aciduria. Biotinidase deficiency can also present in late infancy or preschool years with episodic ataxia, perioral dermatitis, and seizures. This condition is important to recognize, since it can be successfully treated with biotin. Recently, a familial form of episodic cerebellar ataxia has been described that can be due to a problem with cerebellar intracellular pH homeostasis. Some disorders of energy metabolism, as in the case of mitochondrial encephalomyopathy with lactic acidosis and stroke (MELAS) syndrome, can have an intermittent course that includes ataxia. In a number of these disorders, the metabolic defect may only be demonstrable during the clinical episode. Normal metabolic studies obtained when the patient is well should be repeated if another attack occurs.

REFERENCES


