

20 - 450 Ataxic Disorders

450 Ataxic Disorders

The best method to treat human prion diseases may be by reducing PrP, the substrate for PrPSc, rather than trying to directly reduce or eliminate PrPSc. The lifespan of mice is normal when PrPC is reduced or even eliminated; when PRNP is knocked out, mice live a normal span of time with minimal deficits detected, aside from a mild neuropathy. Identification of adults hemizygous for PRNP suggests that humans can also live with reduced levels of PrPC. Currently, antisense oligo nucleotides (ASOs) against PrPC are being tested in symptomatic prion disease. One advantage of treatment methods reducing PrPC is that if they are effective, they should work for all strains and types of human prion disease, as the method is independent of the form of PrPSc that is pathogenic in a given individual. ■ ■ FURTHER READING Aoyagi A et al: A β and tau prion-like activities decline with longevity in the Alzheimer's disease human brain. *Sci Transl Med* 11:eaat8462, 2019. Bizzi A et al: Subtype diagnosis of sporadic Creutzfeldt-Jakob disease with diffusion magnetic resonance imaging. *Ann Neurol* 89:560, 2021. Collinge J: Mammalian prions and their wider relevance in neurodegenerative diseases. *Nature* 539:217, 2016. Geschwind MD: Prion diseases. *Continuum (Minneapolis)* 21:1612, 2015. Hermann P et al: Biomarkers and diagnostic guidelines for sporadic Creutzfeldt-Jakob disease. *Lancet Neurol* 20:235, 2021. Jucker M, Walker LC: Evidence for iatrogenic transmission of Alzheimer's disease. *Nat Med* 30:344, 2024. Kraus A et al: High-resolution structure and strain comparison of infectious mammalian prions. *Mol Cell* 81:4540, 2021. Prusiner SB (ed): *Prion Biology*. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 2017. Prusiner SB (ed): *Prion Diseases*. Cold Spring Harbor, NY, Cold Spring Harbor Laboratory Press, 2017. Prusiner SB et al: Evidence for α -synuclein prions causing multiple system atrophy in humans with parkinsonism. *Proc Natl Acad Sci USA* 112:E5308, 2015. Staffaroni AM et al: Neuroimaging in dementia. *Semin Neurol* 37:510, 2017. Roger N. Rosenberg, Vikram G. Shakkottai

Ataxic Disorders APPROACH TO THE PATIENT Ataxic Disorders Symptoms and signs of ataxia consist of gait impairment, unclear ("scanning") speech, visual blurring due to nystagmus, hand incoordination, and tremor with movement. These result from the involvement of the cerebellum and its afferent and efferent pathways, including the spinocerebellar pathways, and the frontopontocerebellar pathway originating in the rostral frontal lobe. True cerebellar ataxia must be distinguished from ataxia associated with vestibular nerve or labyrinthine disease, as the latter results in a disorder of gait associated with a significant degree of dizziness, light-headedness, or the perception of movement (Chap. 24). True cerebellar ataxia is devoid of these vertiginous complaints and is clearly an unsteady gait due to imbalance. Sensory disturbances can also on occasion simulate the imbalance of cerebellar disease; with sensory ataxia, imbalance dramatically worsens when visual input is

removed (Romberg sign). Rarely, weakness of proximal leg muscles mimics cerebellar disease. In the patient who presents with ataxia, the rate and pattern of the development of cerebellar symptoms help to narrow the diagnostic possibilities (Table 450-1). A gradual and progressive increase in symptoms with bilateral and symmetric involvement suggests a genetic, metabolic, immune, or toxic etiology. Conversely, focal, unilateral symptoms with headache and impaired level of consciousness accompanied by ipsilateral cranial nerve palsies and contralateral weakness imply a space-occupying cerebellar lesion.

SYMMETRIC ATAXIA Progressive and symmetric ataxia can be classified with respect to onset as acute (over hours or days), subacute (weeks or months), or chronic (months to years). Acute and reversible ataxias include those caused by intoxication with alcohol, phenytoin, lithium, barbiturates, and other drugs. Intoxication caused by toluene exposure, gasoline sniffing, glue sniffing, spray painting, or exposure to methyl mercury or bismuth are additional causes of acute or subacute ataxia, as is treatment with cytotoxic chemotherapeutic drugs such as fluorouracil and paclitaxel. Patients with a postinfectious syndrome (especially after varicella) may develop gait ataxia and mild dysarthria, both of which are reversible (Chap. 456). Rare infectious causes of acquired ataxia include poliovirus, coxsackievirus, echovirus, Epstein-Barr virus, toxoplasmosis, Legionella, and Lyme disease.

CHAPTER 450 Ataxic Disorders The subacute development of ataxia of gait over weeks to months (degeneration of the cerebellar vermis) may be due to the combined effects of alcoholism and malnutrition, particularly with deficiencies of vitamins B1 and B12. Hyponatremia has also been associated with ataxia. Paraneoplastic cerebellar ataxia is associated with a number of different tumors (and autoantibodies) such as breast and ovarian cancers (anti-Yo), small-cell lung cancer (anti-PQ-type voltage-gated calcium channel), and Hodgkin's disease (anti-Tr) (Chap. 99). Another paraneoplastic syndrome associated with myoclonus and opsoclonus occurs with breast (anti-Ri) and lung cancers and neuroblastoma. For all of these paraneoplastic ataxias, the neurologic syndrome may be the presenting symptom of the cancer. Autoantibody-associated cerebellar syndromes also occur without a cancer association. The most common is a progressive ataxic syndrome affecting speech and gait associated with serum anti-glutamic acid decarboxylase (GAD65) antibodies (Chap. 99). Another immune-mediated progressive ataxia is associated with antigliadin (and antiendomysium) antibodies and the human leukocyte antigen (HLA) DQB1*0201 haplotype; in some affected patients, biopsy of the small intestine reveals villus atrophy consistent with gluten-sensitive enteropathy (Chap. 336). Finally, subacute progressive ataxia may be caused by a prion disorder, especially when an infectious etiology, such as transmission from contaminated human growth hormone, is responsible (Chap. 449). Chronic symmetric gait ataxia suggests an inherited ataxia (discussed below), a metabolic disorder, or a chronic infection. Hypothyroidism must always be considered as a readily treatable and reversible form of gait ataxia. Infectious diseases that can present with ataxia are meningovascular syphilis and tabes dorsalis due to degeneration of the posterior columns and spinocerebellar pathways in the spinal cord.

FOCAL ATAXIA Acute focal ataxia commonly results from cerebrovascular disease, usually ischemic infarction or cerebellar hemorrhage. These lesions typically produce cerebellar symptoms ipsilateral to the injured cerebellum and may be associated with an impaired level of consciousness due to brainstem compression and increased intracranial pressure; ipsilateral pontine signs, including sixth and seventh nerve palsies, may be present. Focal and worsening signs of acute ataxia should also prompt consideration of a posterior fossa subdural hematoma, bacterial abscess, or primary or metastatic cerebellar

TABLE 450-1 Etiology of Cerebellar Ataxia SYMMETRIC AND PROGRESSIVE SIGNS FOCAL AND IPSILATERAL CEREBELLAR SIGNS SUBACUTE (DAYS

TO WEEKS) CHRONIC (MONTHS

TO YEARS) ACUTE (HOURS TO DAYS) ACUTE (HOURS TO DAYS) Intoxication: alcohol, lithium, phenytoin, barbiturates (positive history and toxicology screen) Acute viral cerebellitis (CSF supportive of acute viral infection) Postinfection syndrome Intoxication: mercury, solvents, gasoline, glue Cytotoxic chemotherapeutic drugs Alcoholic-nutritional (vitamin B1 and B12 deficiency) Lyme disease Paraneoplastic syndrome Antigliadin antibody syndrome Hypothyroidism Inherited diseases Tabes dorsalis (tertiary syphilis) Phenytoin toxicity Amiodarone Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging. PART 13 Neurologic Disorders tumor. Computed tomography (CT) or magnetic resonance imaging (MRI) studies will reveal clinically significant processes of this type. Many of these lesions represent true neurologic emergencies, as sudden herniation, either rostrally through the tentorium or caudal herniation of cerebellar tonsils through the foramen magnum, can occur and is usually devastating. Acute surgical decompression may be required (Chap. 318). Lymphoma or progressive multifocal leukoencephalopathy (PML) in a patient with AIDS may present with an acute or subacute focal cerebellar syndrome. Chronic etiologies of progressive ataxia include multiple sclerosis (Chap. 455) and congenital lesions such as a Chiari malformation (Chap. 453) or a congenital cyst of the posterior fossa (Dandy-Walker syndrome). THE INHERITED ATAXIAS Inherited ataxias may show autosomal dominant, autosomal recessive, or maternal (mitochondrial) modes of inheritance. A genomic classification (Table 450-2)¹ has now largely superseded previous ones based on clinical expression alone. Although the clinical manifestations and neuropathologic findings of cerebellar disease dominate the clinical picture, there may also be characteristic changes in the basal ganglia, brainstem, spinal cord, optic nerves, retina, and peripheral nerves. In large families with dominantly inherited ataxias, many gradations are observed from purely cerebellar manifestations to mixed cerebellar and brainstem disorders, cerebellar and basal ganglia syndromes, and spinal cord or peripheral nerve disease. Rarely, dementia is present as well. The clinical picture may be homogeneous within a family with dominantly inherited ataxia, but sometimes most affected family members show one characteristic syndrome, while one or several members have an entirely different phenotype. ■ ■AUTOSOMAL DOMINANT ATAXIAS The autosomal spinocerebellar ataxias (SCAs) include SCA types 1 through 50, dentatorubropallidoluysian atrophy (DRPLA), and episodic ataxia (EA) types 1 to 7 (Table 450-2). SCA1, SCA2, SCA3 (Machado-Joseph disease [MJD]), SCA6, SCA7, and SCA17 are caused by CAG triplet repeat expansions in different genes. SCA8 is due to an untranslated CTG repeat expansion, SCA12 is linked to an untranslated CAG repeat, and SCA10 is caused by an untranslated pentanucleotide repeat. The clinical phenotypes of these SCAs overlap. The genotype has become the gold standard for diagnosis and classification. CAG encodes glutamine, and these expanded CAG triplet repeat expansions result in expanded polyglutamine proteins, termed ataxins, that produce a toxic gain of function with autosomal dominant inheritance. Although the phenotype is variable for any given disease gene, a pattern of neuronal loss with gliosis is produced that is relatively unique for each ataxia. Immunohistochemical and biochemical studies ¹Table 450-2 can be found online at accessmedicine.com.

SUBACUTE (DAYS

TO WEEKS) CHRONIC (MONTHS

TO YEARS) Vascular: cerebellar infarction, hemorrhage, or subdural hematoma Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion) Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT) Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent) AIDS-related multifocal leukoencephalopathy (positive HIV test and CD4+ cell count for AIDS) Stable gliosis secondary to vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months) Congenital lesion: Chiari or DandyWalker malformations (malformation noted on MRI/CT) have shown cytoplasmic (SCA2), neuronal (SCA1, MJD, SCA7), and nucleolar (SCA7) accumulation of the specific mutant polyglutamine-containing ataxin proteins. Expanded polyglutamine ataxins with more than ~40 glutamines are potentially toxic to neurons for a variety of reasons including the following: high levels of gene expression for the mutant polyglutamine ataxin in affected neurons; conformational change of the aggregated protein to a β -pleated structure; abnormal transport of the ataxin into the nucleus (SCA1, MJD, SCA7); binding to other polyglutamine proteins, including the TATA-binding transcription protein and the CREB-binding protein, impairing their functions; altering the efficiency of the ubiquitin-proteasome system of protein turnover; and inducing neuronal apoptosis. An earlier age of onset (anticipation) and more aggressive disease in subsequent generations are due to further expansion of the CAG triplet repeat and increased polyglutamine number in the mutant ataxin. The most common disorders are discussed below. ■ ■SCA1 SCA1 was previously referred to as olivopontocerebellar atrophy, but genomic data have shown that that entity represents several different genotypes with overlapping clinical features. Symptoms and Signs SCA1 is characterized by the development in early- or middle-adult life of progressive cerebellar ataxia of the trunk and limbs, impairment of equilibrium and gait, slowness of voluntary movements, scanning speech, nystagmoid eye movements, and oscillatory tremor of the head and trunk. Dysarthria, dysphagia, and oculomotor and facial palsies may also occur. Extrapyr amidal symptoms include rigidity, an immobile face, and parkinsonian tremor. The reflexes are usually normal, but knee and ankle jerks may be lost, and extensor plantar responses may occur. Dementia may be noted but is usually mild. Impairment of sphincter function is common, with urinary and sometimes fecal incontinence. Cerebellar and brainstem atrophy are evident on MRI (Fig. 450-1). Marked shrinkage of the ventral half of the pons, disappearance of the olivary eminence on the ventral surface of the medulla, and atrophy of the cerebellum are evident on gross postmortem inspection of the brain. Variable loss of Purkinje cells, reduced numbers of cells in the molecular and granular layer, demyelination of the middle cerebellar peduncle and the cerebellar hemispheres, and severe loss of cells in the pontine nuclei and olives are found on histologic examination. Degenerative changes in the striatum, especially the putamen, and loss of the pigmented cells of the substantia nigra may be found in cases with extrapyramidal features. More widespread degeneration in the central nervous system (CNS), including involvement of the posterior columns and the spinocerebellar fibers, is often present. ■ ■GENETIC CONSIDERATIONS SCA1 encodes a gene product, called ataxin-1, that regulates transcriptional repression with various nuclear factors. As a protein that can bind RNA, ataxin-1 may also regulate gene transcription posttranslationally. The mutant allele has 40 CAG repeats located

FIGURE 450-1 Sagittal magnetic resonance imaging (MRI) of the brain of a 60-yearold man with gait ataxia and dysarthria due to spinocerebellar ataxia type 1 (SCA1), illustrating cerebellar atrophy (arrows). (Reproduced with permission from RN Rosenberg, P Khemani, in RN Rosenberg, JM

Pascual [eds]: Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5th ed. London, Elsevier, 2015.) within the coding region, whereas alleles from unaffected individuals have ≤ 36 repeats. A few patients with 38–40 CAG repeats have been described. There is a direct correlation between a larger number of repeats and a younger age of onset for SCA1. Juvenile patients have higher numbers of repeats, and anticipation is present in subsequent generations. Transgenic mice carrying SCA1 developed ataxia and Purkinje cell pathology. Leucine-rich acidic nuclear protein localization, but not aggregation, of ataxin-1 appears to be required for cell death initiated by the mutant protein. ■ ■ SCA2 Symptoms and Signs Another clinical phenotype, SCA2, has been described in patients from Cuba and India. Cuban patients probably are descendants of a common ancestor, and the population may be the largest homogeneous group of patients with ataxia described. The age of onset ranges from 2 to 65 years, and there is considerable clinical variability within families. Although neuropathologic and clinical findings are compatible with a diagnosis of SCA1, including slow saccadic eye movements, ataxia, dysarthria, parkinsonian rigidity, optic disc pallor, mild spasticity, and retinal degeneration, SCA2 is a unique form of cerebellar degenerative disease. ■ ■ GENETIC CONSIDERATIONS The gene in SCA2 families also contains CAG repeat expansions coding for a polyglutamine-containing protein, ataxin-2. Normal alleles contain 15–32 repeats; mutant alleles have 35–77 repeats. Ataxin-2 has recently been shown to assemble with polyribosomes. Ataxin-2 is also an important risk factor for sporadic amyotrophic lateral sclerosis (ALS). ■ ■ MACHADO-JOSEPH DISEASE/SCA3 MJD was first described among the Portuguese and their descendants in New England and California. Subsequently, MJD has been found in families from Portugal, Australia, Brazil, Canada, China, England, France, India, Israel, Italy, Japan, Spain, Taiwan, and the United States. In most populations, it is the most common autosomal dominant ataxia. Symptoms and Signs MJD has been classified into three clinical types. In type I MJD (ALS-parkinsonism-dystonia type), neurologic deficits appear in the first two decades and involve weakness and spasticity of extremities, especially the legs, often with dystonia of the face, neck, trunk, and extremities. Patellar and ankle clonus are common, as are extensor plantar responses. The gait is slow and stiff, with a slightly broadened base and lurching from side to side; this gait results from spasticity, not true ataxia. There is no truncal titubation. Pharyngeal

weakness and spasticity cause difficulty with speech and swallowing. Of note is the prominence of horizontal and vertical nystagmus, loss of fast saccadic eye movements, hypermetric and hypometric saccades, and impairment of upward vertical gaze. Facial fasciculations, facial myokymia, lingual fasciculations without atrophy, ophthalmoparesis, and ocular prominence are common early manifestations.

In type II MJD (ataxic type), true cerebellar deficits of dysarthria and gait and extremity ataxia begin in the second to fourth decades along with corticospinal and extrapyramidal deficits of spasticity, rigidity, and dystonia. Type II is the most common form of MJD. Ophthalmoparesis, upward vertical gaze deficits, and facial and lingual fasciculations are also present. Type II MJD can be distinguished from the clinically similar disorders SCA1 and SCA2. Type III MJD (ataxic-amyotrophic type) presents in the fifth to seventh decades with a pancerebellar disorder that includes dysarthria and gait and extremity ataxia. Distal sensory loss involving pain, touch, vibration, and position senses and distal atrophy are prominent, indicating the presence of peripheral neuropathy. The deep tendon reflexes are depressed to absent, and there are no corticospinal or extrapyramidal findings. CHAPTER 450 The mean age of onset of symptoms in MJD

is 25 years. Neurologic deficits invariably progress and lead to death from debilitation within 15 years of onset, especially in patients with types I and II disease. Usually, patients retain full intellectual function.

Ataxic Disorders The major pathologic findings are variable loss of neurons and glial replacement in the corpus striatum and severe loss of neurons in the pars compacta of the substantia nigra. A moderate loss of neurons occurs in the dentate nucleus of the cerebellum and in the red nucleus. Purkinje cell loss and granule cell loss occur in the cerebellar cortex. Cell loss also occurs in the dentate nucleus and in the cranial nerve motor nuclei. Sparing of the inferior olives distinguishes MJD from other dominantly inherited ataxias.

■ **GENETIC CONSIDERATIONS** The gene for MJD maps to 14q24.3-q32. Unstable CAG repeat expansions are present in the MJD gene coding for a polyglutamine-containing protein named ataxin-3, or MJD-ataxin. An earlier age of onset is associated with longer repeats. Alleles from normal individuals have between 12 and 37 CAG repeats, whereas MJD alleles have 60–84 CAG repeats. Polyglutamine-containing aggregates of ataxin-3 (MJD-ataxin) have been described in neuronal nuclei undergoing degeneration. MJD-ataxin codes for a ubiquitin protease, which is inactive due to expanded polyglutamines. Proteasome function is impaired, resulting in altered clearance of proteins and cerebellar neuronal loss.

■ **SCA6** Genomic screening for CAG repeats in other families with autosomal dominant ataxia and vibratory and proprioceptive sensory loss have yielded another locus. Of interest is that different mutations in the same gene for the $\alpha 1A$ voltage-dependent calcium channel subunit (CACNL1A4; also referred to as the CACNA1A gene) at 19p13 result in different clinical disorders. CAG repeat expansions (21–27 in patients; 4–16 triplets in normal individuals) result in late-onset progressive ataxia with cerebellar degeneration. Missense mutations in this gene result in familial hemiplegic migraine. Nonsense mutations resulting in termination of protein synthesis of the gene product yield hereditary paroxysmal cerebellar ataxia or EA. Some patients with familial hemiplegic migraine develop progressive ataxia and also have cerebellar atrophy.

■ **SCA7** This disorder is distinguished from all other SCAs by the presence of retinal pigmentary degeneration. The visual abnormalities first appear as blue-yellow color blindness and proceed to frank visual loss with macular degeneration. In almost all other respects, SCA7 resembles several other SCAs in which ataxia is accompanied by various non cerebellar findings, including ophthalmoparesis and extensor plantar responses. The genetic defect is an expanded CAG repeat in the SCA7

gene at 3p14-p21.1. The expanded repeat size in SCA7 is highly variable. Consistent with this, the severity of clinical findings varies from essentially asymptomatic to mild late-onset symptoms to severe, aggressive disease in childhood with rapid progression. Marked anticipation has been recorded, especially with paternal transmission. The disease protein, ataxin-7, forms aggregates in nuclei of affected neurons, as has also been described for SCA1 and SCA3/MJD. Ataxin-7 is a subunit of GCN5, a histone acetyltransferase-containing complex.

■ **SCA8** This form of ataxia is caused by a CTG repeat expansion in an untranslated region of a gene on chromosome 13q21. There is marked maternal bias in transmission, perhaps reflecting contractions of the repeat during spermatogenesis. The mutation is not fully penetrant. Symptoms include slowly progressive dysarthria and gait ataxia beginning at ~40 years of age with a range between 20 and 65 years. Other features include nystagmus, leg spasticity, and reduced vibratory sensation. Severely affected individuals are nonambulatory by the fourth to sixth decades. MRI shows cerebellar atrophy. The mechanism of disease may involve a dominant “toxic” effect occurring at the RNA level, as occurs in myotonic dystrophy.

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■ **SCA27B** SCA27B is a recently discovered entity, resulting from an intronic GAA repeat expansion

in the FGF14 gene, and is one of the most common late-onset inherited ataxias. SCA27B occurs with a median age of onset of 60 years and presents as a relatively pure cerebellar ataxia with episodic symptoms at the disease onset. Other clinical features include afferent sensory deficits and dysautonomia. Cognitive impairment is infrequent. Both the episodic symptoms and symptom severity of ataxia appear to improve with 4-aminopyridine, although randomized clinical trials have not yet been performed in this population. ■ ■ DENTATORUBROPALLOIDAL ATROPHY DRPLA has a variable presentation that may include progressive ataxia, choreoathetosis, dystonia, seizures, myoclonus, and dementia. DRPLA is due to unstable CAG triplet repeats in the open reading frame of a gene named atrophin located on chromosome 12p12-ter. Larger expansions are found in patients with earlier onset. The number of repeats is 49 in patients with DRPLA and ≤ 26 in normal individuals. Anticipation occurs in successive generations, with earlier onset of disease in association with an increasing CAG repeat number in children who inherit the disease from their father. One well-characterized family in North Carolina has a phenotypic variant known as the Haw River syndrome, now recognized to be due to the DRPLA mutation. ■ ■ EPISODIC ATAXIA EA types 1 and 2 are two rare dominantly inherited disorders that have been mapped to chromosomes 12p (a potassium channel gene, KCNA1, Phe249Leu mutation) for type 1 and 19p for type 2. Patients with EA-1 have brief episodes of ataxia with myokymia and nystagmus that last only minutes. Startle, sudden change in posture, and exercise can induce episodes. Acetazolamide or anticonvulsants may be therapeutic. Patients with EA-2 have episodes of ataxia with nystagmus that can last for hours or days. Stress, exercise, or excessive fatigue may be precipitants. Acetazolamide may be therapeutic and can reverse the relative intracellular alkalosis detected by magnetic resonance spectroscopy. Stop codon, nonsense mutations causing EA-2 have been found in the CACNA1A gene, encoding the $\alpha 1A$ voltage-dependent calcium channel subunit (see "SCA6," above). ■ ■ AUTOSOMAL RECESSIVE ATAXIAS Friedreich's Ataxia This is the most common form of inherited ataxia, composing one-half of all hereditary ataxias. It can occur in a classic form or in association with a genetically determined vitamin E deficiency syndrome; the two forms are clinically indistinguishable. SYMPTOMS AND SIGNS Friedreich's ataxia presents before 25 years of age with progressive staggering gait, frequent falling, and titubation. The lower extremities are more severely involved than the upper ones.

Dysarthria occasionally is the presenting symptom; rarely, progressive scoliosis, foot deformity, nystagmus, or cardiopathy is the initial sign. The neurologic examination reveals nystagmus, loss of fast saccadic eye movements, truncal titubation, dysarthria, dysmetria, and ataxia of trunk and limb movements. Extensor plantar responses (with normal tone in trunk and extremities), absence of deep tendon reflexes, and weakness (greater distally than proximally) are usually found. Loss of vibratory and proprioceptive sensation occurs. The median age of death is 35 years. Women have a significantly better prognosis than men. Cardiac involvement occurs in 90% of patients. Cardiomegaly, symmetric hypertrophy, murmurs, and conduction defects are reported. Moderate intellectual disability or psychiatric syndromes are present in a small percentage of patients. A high incidence (20%) of diabetes mellitus is found and is associated with insulin resistance and pancreatic β -cell dysfunction. Musculoskeletal deformities are common and include pes cavus, pes equinovarus, and scoliosis. MRI of the spinal cord shows atrophy (Fig. 450-2). The primary sites of pathology are the spinal cord, dorsal root ganglion cells, and the peripheral nerves. Slight atrophy of the cerebellum and cerebral gyri may occur. Sclerosis and degeneration occur predominantly in the spinocerebellar tracts, lateral corticospinal tracts, and posterior columns. Degeneration of the glossopharyngeal, vagus, hypoglossal, and deep cerebellar nuclei is described. The cerebral cortex

is histologically normal except for loss of Betz cells in the precentral gyri. The peripheral nerves are extensively involved, with a loss of large myelinated fibers. Cardiac pathology consists of myocytic hypertrophy and fibrosis, focal vascular fibromuscular dysplasia with subintimal or medial deposition of periodic acid-Schiff (PAS)-positive material, myocytopathy with unusual pleomorphic nuclei, and focal degeneration of nerves and cardiac ganglia. ■ ■ GENETIC CONSIDERATIONS The classic form of Friedreich's ataxia has been mapped to 9q13q21.1, and the mutant gene, frataxin, contains expanded GAA triplet repeats in the first intron. There is homozygosity for expanded GAA repeats in >95% of patients. Normal persons have 7–22 GAA repeats, and patients have 200–900 GAA repeats. A more varied clinical syndrome has been described in compound heterozygotes who have one copy of the GAA expansion and the other copy a point mutation in the frataxin gene. When the point mutation is located in the region of the gene that encodes the amino-terminal half of frataxin, the phenotype is milder, often consisting of a spastic gait, retained or exaggerated reflexes, no dysarthria, and mild or absent ataxia. Patients with Friedreich's ataxia have undetectable or extremely low levels of frataxin mRNA, as compared with carriers and unrelated

FIGURE 450-2 Sagittal magnetic resonance imaging (MRI) of the brain and spinal cord of a patient with Friedreich's ataxia, demonstrating spinal cord atrophy. (Reproduced with permission from RN Rosenberg, P Khemani, in RN Rosenberg, JM Pascual [eds]: Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5th ed. London, Elsevier, 2015.)

individuals; thus, disease appears to be caused by a loss of expression of the frataxin protein. Frataxin is a mitochondrial protein involved in iron homeostasis. Mitochondrial iron accumulation due to loss of the iron transporter coded by the mutant frataxin gene results in a deficiency in iron/sulfur clusters containing mitochondrial enzymes, decreased ATP production, and accumulation of iron in the heart. Excess oxidized iron results in turn in the oxidation of cellular components and irreversible cell injury. Two forms of hereditary ataxia associated with abnormalities in the interactions of vitamin E (α -tocopherol) with very-low-density lipoprotein (VLDL) have been delineated. These are abetalipoproteinemia (Bassen-Kornzweig syndrome) and ataxia with vitamin E deficiency (AVED). Abetalipoproteinemia is caused by mutations in the gene coding for the larger subunit of the microsomal triglyceride transfer protein (MTP). Defects in MTP result in impairment of formation and secretion of VLDL in liver. This defect results in a deficiency of delivery of vitamin E to tissues, including the central and peripheral nervous system, as VLDL is the transport molecule for vitamin E and other fat-soluble substitutes. AVED is due to mutations in the gene for α -tocopherol transfer protein (α -TTP). These patients have an impaired ability to bind vitamin E into the VLDL produced and secreted by the liver, resulting in a deficiency of vitamin E in peripheral tissues. Hence, either absence of VLDL (abetalipoproteinemia) or impaired binding of vitamin E to VLDL (AVED) causes an ataxic syndrome. Once again, a genotype classification has proved to be essential in sorting out the various forms of the Friedreich's disease syndrome, which may be clinically indistinguishable. RFC1-Related CANVAS Syndrome Biallelic intronic AAGGG repeat expansions in the replication factor C subunit 1 (RFC1) gene are the cause of late-onset ataxia, particularly if associated with sensory neuronopathy and bilateral vestibular areflexia (CANVAS syndrome). A chronic unexplained cough is often associated with and may precede the onset of neurologic symptoms. Ataxia Telangiectasia • SYMPTOMS AND SIGNS Patients with ataxia telangiectasia (AT) present in the first decade of life with progressive telangiectatic lesions associated with deficits in cerebellar function and nystagmus. The neurologic manifestations correspond to those in Friedreich's disease, which should be included in the differential diagnosis. Truncal and limb ataxia, dysarthria, extensor plantar responses, myoclonic jerks, areflexia, and

distal sensory deficits may develop. There is a high incidence of recurrent pulmonary infections and neoplasms of the lymphatic and reticuloendothelial system in patients with AT. Thymic hypoplasia with cellular and humoral (IgA and IgG2) immunodeficiencies, premature aging, and endocrine disorders such as type 1 diabetes mellitus are described. There is an increased incidence of lymphomas, Hodgkin's disease, acute T-cell leukemias, and breast cancer. The most striking neuropathologic changes include loss of Purkinje, granule, and basket cells in the cerebellar cortex as well as of neurons in the deep cerebellar nuclei. The inferior olives of the medulla may also have neuronal loss. There is a loss of anterior horn neurons in the spinal cord and of dorsal root ganglion cells associated with posterior column spinal cord demyelination. A poorly developed or absent thymus gland is the most consistent defect of the lymphoid system. ■ ■

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The gene for AT (the ATM gene) at 11q22-23 encodes a protein that is similar to several yeast and mammalian phosphatidylinositol-3' kinases involved in mitogenic signal transduction, meiotic recombination, and cell cycle control. Defective DNA repair in AT fibroblasts exposed to ultraviolet light has been demonstrated. The discovery of ATM permits early diagnosis and identification of heterozygotes who are at risk for cancer (e.g., breast cancer). Elevated serum alpha-fetoprotein and immunoglobulin deficiency are noted. ■ ■

MITOCHONDRIAL ATAXIAS Spinocerebellar syndromes have been identified with mutations in mitochondrial DNA (mtDNA). Thirty pathogenic mtDNA point mutations and 60 different types of mtDNA deletions are known, several of which cause or are associated with ataxia (Chap. 460).

TREATMENT Ataxic Disorders The most important goal in management of patients with ataxia is to identify treatable disease entities. Mass lesions must be recognized promptly and treated appropriately. Autoimmune paraneoplastic disorders can often be identified by the clinical patterns of disease that they produce, measurement of specific autoantibodies, and uncovering the primary cancer; these disorders are often refractory to therapy, but some patients improve following removal of the tumor or immunotherapy (Chap. 99). Ataxia with antigliadin antibodies and gluten-sensitive enteropathy may improve with a gluten-free diet. Malabsorption syndromes leading to vitamin E deficiency may lead to ataxia. The vitamin E deficiency form of Friedreich's ataxia must be considered, and serum vitamin E levels measured. Vitamin E therapy is indicated for these rare patients. Vitamin B1 and B12 levels in serum should be measured, and the vitamins administered to patients having deficient levels. Hypothyroidism is easily treated. The cerebrospinal fluid should be tested for a syphilitic infection in patients with progressive ataxia and other features of tabes dorsalis. Similarly, antibody titers for Lyme disease and Legionella should be measured and appropriate antibiotic therapy should be instituted in antibody-positive patients. Aminoacidopathies, leukodystrophies, urea-cycle abnormalities, and mitochondrial encephalomyopathies may produce ataxia, and some dietary or metabolic therapies are available for these disorders. The deleterious effects of phenytoin and alcohol on the cerebellum are well known, and these exposures should be avoided in patients with ataxia of any cause. **CHAPTER 450 Ataxic Disorders** There is no proven therapy for any of the autosomal dominant ataxias (SCA1 to SCA43). Omaveloxolone, a NRF2 agonist, is the only U.S. Food and Drug Administration-approved agent for Friedreich's ataxia. NRF2 is a transcription factor that regulates gene transcripts involved in mitochondrial energy production and addresses the root cause of mitochondrial dysfunction in Friedreich's ataxia. Iron chelators and antioxidant drugs are potentially harmful in Friedreich's patients because they may increase heart muscle injury. Acetazolamide can reduce the duration of symptoms of EA. At present, identification of an at-risk person's genotype, together with

appropriate family and genetic counseling, can reduce the incidence of these cerebellar syndromes in future generations (Chap. 480). ■ ■ GENETIC DIAGNOSTIC LABORATORIES

1. Baylor College of Medicine; Houston, Texas, 1-713-798-6522

<http://www.bcm.edu/genetics/index.cfm?pmid=21387> 2. The University of Chicago Genetic Services Laboratories

<https://dnatesting.uchicago.edu> 3. GeneDx

<http://www.genedx.com> 4. Transgenomic, 1-877-274-9432

<http://www.transgenomic.com/labs/neurology> ■ ■ GLOBAL FEATURES Ataxias with autosomal dominant, autosomal recessive, X-linked, or mitochondrial forms of inheritance are present on a worldwide basis. MJD (SCA3) (autosomal dominant) and Friedreich's ataxia (autosomal recessive) are the most common types in most populations. Genetic markers are now commercially available to precisely identify the genetic mutation for correct diagnosis and also for family planning. Early detection of asymptomatic preclinical disease can reduce or eliminate the inherited form of ataxia in some families on a global, worldwide basis.

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