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Ataxia

Umar Akbar, M.D. and Tetsuo Ashizawa, M.D.

Department of Neurology and the Center for Movement Disorders and Neurorestoration, College of Medicine, and, McKnight Brain Institute, University of Florida

Abstract

Balance and coordination are products of complex circuitry involving the basal ganglia, cerebellum and cerebral cortex, as well as peripheral motor and sensory pathways. Malfunction of any part of this intricate circuitry can lead to imbalance and incoordination, or ataxia, of gait, the limbs or eyes, or a combination thereof. Ataxia can be a symptom of a multisystemic disorder, or it can manifest as the major component of a disease process. Ongoing discoveries of genetic abnormalities suggest the role of mitochondrial dysfunction, oxidative stress, abnormal mechanisms of DNA repair, possible protein misfolding, and abnormalities in cytoskeletal proteins. Few ataxias are fully treatable, and most are symptomatically managed. A discussion of the ataxias is presented here with brief mention of acquired ataxias, and a greater focus on inherited ataxias.

Introduction

Complex circuitry connecting the basal ganglia, cerebellum and cerebral cortex is involved in producing coordinated movements of the eyes and limbs. Malfunction of any part of this intricate circuitry can lead to incoordination, or ataxia, of gait, the limbs or eyes, or a combination thereof. Afferent inputs into the motor circuitry are also critical in production of coordinated movements, and disruptions in sensory pathways can produce incoordination known as sensory ataxia. Ataxia can be acquired, inherited or sporadic (lacking a definite genetic defect or acquired etiology). This review focuses on the inherited ataxias, their clinical presentation, pathophysiology and available treatments, with a quick overview of acquired ataxias.

Acquired Ataxias

Vascular insults, including strokes and global anoxic events, tumors, trauma and demyelinating disease (i.e. multiple sclerosis) are common causes of acquired ataxia. Other causes include congenital anomalies, infection, autoimmunity and vitamin deficiencies. Detailed history and examination, imaging studies and other corroborating tests often

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Corresponding Author: Tetsuo Ashizawa, M.D., 1149 S Newell Dr, L3-100, Gainesville, Florida 32611.

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confirm the etiology in these cases. Hypothyroidism can occasionally cause mild disequilibrium and gait ataxia with pathology in the midline cerebellar structures.¹ Symptoms can be dramatically improved with timely recognition and thyroid replacement.² Alcohol is a major toxic cause of ataxia and excessive use leads to degeneration of the midline cerebellum. Progressive trunk and gait ataxia is characteristic, with little involvement of upper limbs, eyes or speech (a corollary of relative cerebellar hemispheric sparing). Over a year of abstinence can improve ataxia drastically.³ Chemotherapy agents, especially 5-fluorouracil (5FU) and cytosine arabinoside (ara-C), can cause a cerebellar syndrome particularly in higher-than-conventional doses.⁴ Supratherapeutic serum levels of anti-epilepsy drugs (AEDs), particularly phenytoin, are associated with acute reversible dose-dependent cerebellar signs, and permanent ataxia may emerge with chronic use. All but two AEDs (gabapentin and levetiracetam) were shown in a meta-analysis to have higher and dose-dependent risk of imbalance.⁵ Heavy metals can also cause ataxia. Paresthesias, ataxia and visual field defect can be seen in organic mercury exposure. Lead poisoning, particularly in children, is typically associated with encephalopathy and abdominal colic, but ataxia can be a prominent presenting feature. Chelation therapy has been reported to successfully restore neurological function.⁶ Excessive use of bismuth subsalicylate (Pepto-Bismol) can cause bismuth toxicity which is associated with ataxic gait, myoclonus and confusion.⁷ Abuse of paint-products that contain toluene may lead to persistent ataxia, cognitive impairment, and pyramidal tract signs.⁸

Ataxia can be caused by infectious or post-infectious syndromes involving the cerebellum, brainstem, or both. Neuroimaging, serology, and cerebrospinal fluid (CSF) analysis can help identify the etiology. Combination of ophthalmoplegia, ataxia and other cranial nerve deficits is suggestive of Bickerstaff encephalitis.⁹ Ataxia can be one of many neurological symptoms in human immunodeficiency virus (HIV) infection. Rapidly progressive ataxia and dementia can be seen in Creutzfeldt-Jakob disease. Ataxia is a more common CNS symptom of Whipple's disease than the pathognomonic feature of oculomasticatory myorhythmia.¹⁰ The condition, which is otherwise fatal, should be promptly diagnosed using brain imaging, CSF assays and duodenal biopsies, and treated with antibiotics.¹⁰

Paraneoplastic cerebellar degeneration is one of several autoimmune causes of ataxia, and can be associated with other CNS signs including dysarthria, oscillopsia, dementia and extrapyramidal signs.¹¹ Thorough neoplasia workup should be performed, as cancer treatment can improve the ataxia. Anti-purkinje cell antibodies, such as anti-Yo, Hu, and Ri antibodies, may be detectable. The combination of ataxia, hyperreflexia and peripheral neuropathy is seen in Celiac disease due to gluten sensitivity. A dietary restriction of gluten can improve symptoms once the diagnosis is confirmed with antibody testing and small-bowel biopsy.¹²

Anti-GAD ataxia

Antibodies against glutamic acid decarboxylase (GAD) have been reported in patients with progressive ataxia.¹³ The affected are typically adult females who present with ataxia, nystagmus and dysarthria, and develop antibodies against thyroid, parietal cells and pancreatic islet cells, the latter leading to insulin-dependent diabetes. GAD is instrumental in

synthesizing gamma-aminobutyric acid (GABA) from glutamate, and the antibodies are thought to pathologically bind to GABA terminals. Antibody testing is commercially available and symptoms may be improved with intravenous immunoglobulins and immunosuppressive agents.¹⁴⁻¹⁷

Superficial siderosis

Concealed bleeding in the brain can lead to iron and hemosiderin accumulation in the pial and subpial areas causing superficial siderosis, which manifests with ataxia, deafness and cognitive dysfunction.¹⁸ T2-weighted MRI shows characteristic hypointensity over the brain structures. Treatment of the source of bleeding can control the disease.¹⁹

Inherited Ataxias

Autosomal Recessive ataxias

Most autosomal recessive ataxias begin during childhood or early adulthood but onset later in life is also possible. Two defective copies of the gene (one from each parent) are required to manifest symptoms; thus, parents as carriers are usually asymptomatic. Parental consanguinity increases the risk of heritability but is not a requisite. Most patients present singly, without other affected family members. Advances in whole exome and whole genome sequencing provide an opportunity for the identification of causative recessive genes, especially in cases of consanguinity.

Friedreich Ataxia—Nicholas Friedrich described siblings with an ataxia syndrome in the late 19th century and recognized the possibility of a genetic cause.²⁰ That syndrome, now called Friedrich ataxia (FA), is the most common inherited ataxia, typically beginning in childhood, and presenting with gait ataxia, clumsiness, sensory neuropathy, areflexia and eye movement abnormalities.²¹ As disease progresses, dysarthria, dysphagia, and lower extremity weakness become more apparent, and complete loss of ambulation occurs 9-15 years after symptom onset. Skeletal deformities and hypertrophic cardiomyopathy are common extra-neurological symptoms, and glucose intolerance, deafness and optic atrophy occur less frequently.²¹ This clinical picture results from the degeneration of dorsal root ganglion cells, dorsal column and spinocerebellar tracts, dentate nucleus and corticospinal tract. Cerebellar Purkinje cells are spared. No abnormalities of the cerebellum are seen on MRI but atrophy of the upper cervical cord and density changes of the posterior columns may be seen.²²

In FA, the nuclear *FXN* gene on chromosome 9q13-21.1 which codes for the mitochondrial protein frataxin is mutated by a homozygous expansion of the GAA repeat in intron 1.²³ The mutation decreases the transcription of *FXN*, which results in reduced levels of the frataxin protein.²⁴ Normal alleles have 5 to 33 GAA repeats, while 66 to over 1000 repeats are seen in expanded alleles. Prior to the discovery of the FA gene mutation, onset before age 25 years and presence of reflexes were considered exclusionary diagnostic criteria, but late-onset FA (LOFA) and FA with retained reflexes (FARR) have been recognized.²⁵ Other phenotypic variations have been documented, including chorea, myoclonus, pure sensory ataxia and isolated cardiomyopathy, but their mechanisms remain unknown.^{26,27}

Although its exact role is unclear, frataxin is thought to be involved in transfer of iron from the mitochondria to various proteins which contain iron-sulfur (Fe-S) clusters. Fe-S cluster biogenesis depends strongly on frataxin, whose deficiency leads to iron accumulation in the mitochondria, respiratory chain dysfunction and increased oxidative stress.²¹

Symptomatic and supportive treatments are the mainstay for patients with FA. The risk of aspiration due to dysphagia, glucose intolerance and diabetes, and cardiomyopathy require routine screening and close monitoring. Several antioxidants and iron chelators have been studied in FA. Idebenone has been shown to improve cardiomyopathy in one study,²⁸ but had no effect on cardiac function in another study.²⁹ A 6-month phase-III study of idebenone showed no improvement in neurological function although the longer follow up open-label data demonstrated significant improvement.^{30,31} Alpha-tocopherolquinone is an antioxidant which has shown dose-dependent neurological improvement in FA.³⁰ Erythropoietin in a pilot study demonstrated safety and tolerability, but failed to show any neurological improvement.³¹ Idebenone combined with deferiprone in an open-labeled study did not show neurological improvement.³² An open-label pilot study of resveratrol did not show improvement in frataxin levels but high-dose group showed improvement in neurological and speech functions.³³ In an 8-week follow up study, riluzole showed a modest improvement in ataxia scores in a mixed population of patients with various ataxias, including a small number of FA patients.³⁴ Two single doses of epoetin alpha administered in FA patients demonstrated no acute effects of frataxin levels, but did show delayed elevation of frataxin, along with safety and tolerability.³⁵ Most recently, a trial of nicotinamide (vitamin B3) showed no significant clinical improvement in FA symptoms but did show increase in the levels of frataxin proportional to dose-escalation.³⁶

Trials of the following agents are underway or have been recently completed and are yet unpublished (ClinicalTrials.gov): carbamylated erythropoietin, deferiprone, acetyl-L-carnitine, EPI-743 (redox modulating agent), pioglitazone, epoetin alpha, interferon-gamma 1b, EGb761, VP20629 (naturally-occurring antioxidant), and RG2833 (Pandolfo, personal communication).

Ataxia with isolated vitamin E deficiency—Ataxia with isolated vitamin E deficiency (AVED) is related to mutation in the gene encoding the alpha-tocopherol transfer protein (*TTP1*) on chromosome 8.³⁷ The deficiency of vitamin E is not due to poor intestinal absorption, rather related to dysfunction of hepatic processing. Vitamin E has antioxidant properties and its deficiency can cause neurodegeneration, with ataxia. Similar to FA, patients present with ataxia, areflexia and polyneuropathy, but glucose intolerance and cardiomyopathy occur less frequently than in FA.^{24,38} Due to the role of vitamin E in vision, retinitis pigmentosa and visual loss can also be seen. Childhood-onset sporadic ataxia should trigger testing of vitamin E level, and the level is typically less than 1.8 mg/L. Replacement of vitamin E with large doses can stabilize neurological function and even prevent the onset of neurological symptoms, particularly with early initiation of therapy.^{39,40}

Abetalipoproteinemia (Bassen Kornzweig disease)—The *MTTP* gene on chromosome 4 encodes a large subunit of microsomal triglyceride transfer protein. Mutations in this gene, as seen in abetalipoproteinemia, cause malabsorption of lipid and

lipid-soluble vitamins (i.e. vitamins A, D, E, K); thus, the clinical presentation is similar to AVED but with evidence of malabsorption.⁴¹ Blood levels reveal low vitamin E and cholesterol, absent apolipoprotein B, presence of acanthocytes in peripheral smear, and elevated transaminases and INR. Modifying the diet and replacing vitamins may prevent neurological deterioration.

Cayman Ataxia—Cayman ataxia was first identified in the Grand Cayman Island and is related to a mutation in the *ATCAY* gene on chromosome 19, encoding for the caytaxin protein, which plays a role in synaptogenesis of cerebellar granular and purkinje cells and glutamate synthesis. Affected patients carry two homozygous mutations,⁴² and present with developmental delay, early-onset hypotonia and non-progressive axial cerebellar ataxia. Treatment is supportive.

Ataxia-Telangiectasia—With an estimated prevalence of 1 in 20,000 to 100,000 live births,⁴³ ataxia-telangiectasia (AT) is the most common cause of recessive ataxia in patients under age 5 years. Children typically present during the first decade of life with progressive ataxia and oculocutaneous telangiectasias. Polyneuropathy, hypotonia, areflexia and oculomotor apraxia develop as disease progresses. Telangiectasias are found most frequently on the conjunctivae and can also occur in other locations, including the earlobes and popliteal fossa. AT patients can have immunodeficiency which often manifests as recurrent bronchopulmonary infections. AT is also associated with radiation sensitivity and increased risk of malignancies, especially of hematologic origin.

Numerous recognized mutations of the *ATM* gene on chromosome 11 have been associated with AT. Although defective DNA repair of double-strand breaks (DSBs) is thought to be the main cause of AT,⁴⁴ the exact role of *ATM* in pathogenesis of ataxia is unknown. The *ATM* protein, a serine-threonine kinase, responds to DNA damage by initiating phosphorylation of downstream proteins in the signal cascade.^{45,46}

Atrophy of the cerebellum can be seen on brain imaging and blood tests reveal low levels of immunoglobulin (Ig) A, IgM, and IgE, lymphocytopenia and elevated alpha fetoprotein (AFP). The confirmatory test of choice is immunoblot analysis for the *ATM* protein which shows no, or trace, amount of protein in AT patients.

Clinical management is supportive and includes thorough screening and close monitoring for infections and malignancies, and avoiding radiation exposure. Chronic intermittent infusions of immunoglobulins can be tried in patients with recurrent infections, along with other experimental therapeutic agents, including antioxidants,⁴⁷⁻⁴⁹ betamethasone⁵⁰ and dexamethasone.⁵¹

Ataxia-Telangiectasia-like disorder—Mutation of another protein involved in repair of DNA double-strand breaks, *MRE11*, located on chromosome 11 in proximity to the *ATM* gene,⁵² can cause a rare disorder called ataxia-telangiectasia-like (ATL) disorder. Clinical presentation is of early onset with slowly progressive ataxia and oculomotor apraxia. The disease course is milder than in AT. Elevation of serum AFP and telangiectasias are typically absent in ATL.^{53,54}

Ataxias with oculomotor apraxia (AOAs)—Ataxias with oculomotor apraxia (AOAs) are the most common recessive ataxias with childhood onset and typically present with characteristic eye movement abnormality. Oculomotor apraxia is the impairment of saccade initiation and cancellation of vestibulo-ocular reflex resulting in hypometric saccades and defective control of voluntary eye movements. To date, no disease-specific treatments are available.

Ataxia with oculomotor apraxia, type 1 (AOA1)—Onset of AOA1 is usually less than 10 years of age with motor symptoms similar to AT. Slowly progressive ataxia of gait, oculomotor apraxia, polyneuropathy, areflexia followed by dysarthria and upper extremity ataxia are seen in AOA1. Impaired cognition, choreoathetosis, and dystonia may also be seen. Gradual progression of axonal neuropathy eventually leads to severe motor disability with weakness and wasting. Skeletal deformities may ensue. Most children become wheelchair bound by adolescence with loss of independent ambulation 7 to 10 years after onset. It is the most common recessive ataxia in Japan and second most frequent (after FA) in Portugal.^{55,56}

AOA1 is related to mutations in the aprataxin (*APTX*) gene, which encodes a protein involved in DNA single-strand break repair.⁵⁷ Despite the role of *APTX* in DNA repair, AOA1 patients are not at higher risk for malignancies or hypersensitive to radiation.⁵⁸ Laboratory studies demonstrate hypoalbuminemia and hypercholesterolemia, increased creatine kinase (CK), and no elevation in AFP.

Ataxia with oculomotor apraxia, type 2 (AOA2)—Oculomotor apraxia is seen in about half of the cases of AOA2,^{55,57} which is also called spinocerebellar ataxia, recessive 1 (SCAR1). Other features associated with AOA2 include axonal neuropathy, cerebellar atrophy and elevated AFP.⁵⁵ Dystonia, chorea, upper motor neuron signs, head tremor and strabismus can also be seen. Elevated serum CK and hypogonadotropic hypogonadism is rare. Other extra-neurological involvement is not present. Disease onset is usually in the teens and progresses to loss of independent ambulation within 15 years.

AOA2 is associated with mutations in *SETX* gene on chromosome 9, which encodes the senataxin protein.⁵⁷ Senataxin is a DNA/RNA helicase which is involved in coordinating DNA replication, transcription, homologous recombination, meiotic sex chromosome inactivation, and DNA damage response.⁵⁹ In general, defective *SETX* gene leads to the disruption of genomic integrity. A less severe form of AOA2 can be seen with missense mutations in the helicase domain (HD) than in other mutations, while truncating and missense mutations outside of the HD may be related to severe motor neuropathy.⁵⁵ Particular dominant mutations in the *SETX* gene can lead to a familial form of juvenile amyotrophic lateral sclerosis (ALS), and two missense mutations can cause a dominant ataxia syndrome.⁶⁰ AOA was also seen in a family with a homozygous missense mutation in the *PIK3R5* gene.⁶¹

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)—In 1978, Bouchard was the first to identify a recessive spastic ataxia in children in the Charlevoix-Saguenay region of Quebec, Canada.⁶² Since that description, ARSACS has

been reported in Japan, Europe, the USA, Brazil, North Africa and Turkey.^{63,64} Disease onset is usually in the first decade and presents with spasticity followed by ataxia, polyneuropathy, and amyotrophy of distal muscles.⁶⁵ Since the progression is slow, patients often live into the 50s. ARSACS is caused by over 70 mutations of the SACS gene on chromosome 13 which encodes a large chaperone protein, saccin. The involvement of saccin in the ubiquitin-proteasome pathway is suggested by its extensive homology with HSP90 and the N-terminus containing a ubiquitin-like domain.⁶⁶ Saccin is also noted to localize to the mitochondria and plays a role in mitochondrial fission by interacting with dynamin-related protein 1.⁶⁷ In addition to the CNS, saccin is highly expressed in skin, skeletal muscle and pancreas. Variations in phenotype have occurred with association of unusual features including epilepsy,⁶⁸ supranuclear ophthalmoplegia, skin lipofuscin deposits,⁶⁹ autonomic dysfunction,⁷⁰ straightening of the dorsal spine,⁷¹ and cognitive-behavioral dysfunction.⁷²

Cervical spinal cord, cerebral cortex and vermal atrophy is seen on MRI, with hyperintensities in the lateral pons with middle cerebellar peduncle thickening.⁷³ Tractography reveals axonal degeneration of the pyramidal tracts and widespread demyelination of the white matter.⁷⁴ Treatment is limited to supportive therapies. Muscle relaxants orally or by intrathecal delivery can be used for spasticity.

Infantile-onset Spinocerebellar Ataxia (IOSCA)—IOSCA is a severe ataxia syndrome presenting soon after the first year of life with ataxia, hypotonia, athetosis and areflexia. Similar to Alpers-Huttenlocher syndrome caused by *POLG* mutations, IOSCA can present with early-onset encephalopathy with liver dysfunction.⁷⁵ With progression, ophthalmoplegia, sensorineural hearing loss, axonal neuropathy, epilepsy and optic atrophy may emerge. White matter changes, cerebellar cortical atrophy, thinning of the cervical spinal cord, and hyperintensities in the dentate nuclei and surrounding the fourth ventricle are seen on MRI.⁷⁶

The culprit in IOSCA is a mutation in the gene *C10orf2* which codes the twinkle protein, a mitochondrial helicase that participates in DNA replication, and a splice variant known as *twinky* on chromosome 10.⁷⁷ Twinkle catalyzes ATP-dependent 5'→3' unwinding of the duplex DNA,⁷⁸ and pairs with the mitochondrial DNA (mtDNA) polymerase gamma (*POLG*) to create a processive replication machinery for single-stranded DNA (ss-DNA) synthesis.⁷⁹ The carboxy terminal part of Twinkle is crucial for mtDNA helicase function,⁸⁰ while the N-terminal portion is essential for efficient binding to ssDNA.⁸¹ Defects in these regions disrupt both helicase activity and functional efficacy of the mtDNA replisome.⁸¹ Dominant mutations of the *C10orf2* gene have been reported with autosomal dominant progressive external ophthalmoplegia (adPEO)⁸² and sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO).⁸³

Refsum's disease—Buildup of phytanic acid, a branched chain fatty acid, in blood and other tissues leads to a peroxisomal disorder called Refsum's disease (RD). RD is distinct from *infantile Refsum's disease* (peroxisome biogenesis disorder) which manifests with sensorineural deafness, mental and growth retardation, hypotonia, atypical retinitis pigmentosa, facial dysmorphism, and hepatomegaly.⁸⁴ RD, on the other hand, is caused by

mutation in the gene encoding phytanoyl-CoA hydroxylase (*PHYH*) on chromosome 10 and is characterized by cerebellar ataxia, retinitis pigmentosa, sensorineural deafness, polyneuropathy, anosmia, skeletal abnormalities, ichthyosis, renal failure, elevated CSF protein, and cardiac myopathy and arrhythmias.^{85,86} Symptoms typically begin in childhood or adolescence, but adulthood onset can also be seen.

Dietary modifications can decrease attacks and acute attacks can be treated with plasma exchange to lower plasma phytanic acid levels.^{86,87}

Cerebrotendinous Xanthomatosis (CTX)—CTX is a rare lipid-storage disease caused by mutations in the *CYP27A1* gene on chromosome 2 which codes for sterol 27-hydroxylase.^{88,89} The deficiency of this enzyme leads to elevated plasma levels of cholestanol, a cholesterol derivative, and its accumulation in tissues including the brain, tendons and lungs. During the first decade of life, children present with diarrhea, hepatitis, jaundice, pale optic disk, cataracts, premature retinal senescence, and hypermyelinated retinal nerve fibers. By their teens and 20s, patients develop xanthomas, typically on Achilles tendon or patella, hand, elbow and neck tendons, and neurological symptoms including pyramidal signs, ataxia, epilepsy, polyneuropathy, cognitive impairment, and psychiatric problems. Rare features include myoclonus, dystonia and parkinsonism.⁹⁰⁻⁹² Cerebellar ataxia is seen in most patients.⁹³ The xanthomas and early atherosclerosis can be distinguished from other conditions by the presence of cataracts and progressive neurological symptoms.⁹⁴ Elevated levels of cholestanol in the serum and tendons can help with confirming the diagnosis. Serum cholesterol levels are in the low-normal range in CTX. Clinical deterioration can be prevented by prompt treatment with cholic acid, or chenodeoxycholic acid. A 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitor can be used alone or in combination with cholic acid.^{95,96}

Marinesco-Sjogren Syndrome (MSS)—MSS is a recessive disorder characterized primarily by cerebellar ataxia, congenital cataracts, delayed psychomotor maturation, and myopathy associated with progressive muscle weakness.⁹⁷ Other associated features are skeletal deformities, short stature and hypogonadotropic hypogonadism.⁹⁸ The responsible gene is *SIL1* on chromosome 5 which encodes a nucleotide exchange factor for the heat shock protein 70 chaperone HSPA5.⁹⁹ A defect in *SIL1* function leads to the accumulation of potentially cytotoxic unfolded proteins.¹⁰⁰ Although *SIL1* is the only gene associated with MSS, some patients with the typical MSS phenotype have been reported without *SIL1* mutations.¹⁰¹ A genetically distinct entity, congenital cataracts, facial dysmorphism, and neuropathy (CCFDN) is caused by mutation in *CTDP1* gene on chromosome 18. The two disorders share common features including cataracts, ataxia and psychomotor delay.¹⁰² Brain MRI in MSS reveals vermian atrophy and hyperintensities of the cerebellar cortex.^{103,104} Cerebellar cortical atrophy is seen on brain pathology, along with vacuolated purkinje cells. Muscle pathology demonstrates myopathic changes and electronmicroscopic findings of autophagic vacuoles, membranous whorls, and electron-dense double-membrane structures associated with nuclei.¹⁰⁵⁻¹⁰⁷

Clinical management is symptomatic, and includes surgical removal of the cataracts and hormonal replacement for the hypogonadism.

SeSAME syndrome (seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance)—SeSAME syndrome is characterized by

infancy-onset generalized seizures, sensorineural hearing loss, ataxia and psychomotor developmental delay associated with electrolyte abnormalities.¹⁰⁸ Intention tremor, lower extremity weakness and axonal neuropathy can also be seen. Deafness typically manifests by 18-months. K⁺ channel mutation of the *KCNJ10* gene on chromosome 1 is responsible for this rapidly progressive disorder which causes complete loss of ambulation in children by age 6 years.^{108,109} Cerebellar atrophy is visible on brain imaging and laboratory studies demonstrate abnormalities of potassium, pH, magnesium, calcium, plasma renin and aldosterone levels, and urinary loss of potassium, sodium and magnesium.

SYNE1 ataxia (also known as spinocerebellar ataxia, autosomal recessive (SCAR) 8, recessive ataxia of Beauce, autosomal recessive cerebellar ataxia (ARCA) 1)—In multiple French-Canadian families from the Beauce region of Quebec,

affected members were found to have mutations in the *SYNE1* gene on chromosome 6 encoding a structural protein which is a member of the spectrin family.¹¹⁰ Symptoms begin in young-adulthood with progressive ataxia, mild eye movement abnormalities, hyper-reflexia and dysarthria. Four unique homozygous mutations in *SYNE1* were seen in a Japanese family of consanguineous parents. Their phenotype was similar to that of the Canadian families with pure cerebellar atrophy on neuroimaging, and EMG and NCS were unremarkable. One of the Japanese patients developed a slowly progressive upper and lower motor neuron disease at 6 years and developed ataxia at age 19 years.¹¹¹ EMG of this patient showed chronic denervation throughout and MRI revealed atrophy of the cerebellum and brain stem.

Coenzyme Q10 deficiency (also known as autosomal recessive cerebellar ataxia (ARCA) 2)—Coenzyme Q10 (CoQ10) deficiency is a rare, clinically heterogenous

disorder caused by a mutation in any gene associated with synthesis of coenzyme Q. Five major phenotypes have been described including encephalomyopathy with seizures and ataxia; a multisystemic infantile type with encephalopathy, cardiomyopathy and renal syndrome; an ataxic type with cerebellar atrophy; Leigh syndrome with growth retardation; and a myopathic form.¹¹² In the ataxic form, ataxia and cerebellar atrophy beginning in childhood is seen with markedly low levels of CoQ10 in muscle biopsy along with lactic acidemia, elevated serum CK, and episodic myoglobinemia. Other features include myoclonus, seizures, mental retardation, muscle weakness, fatigability, hyporeflexia, and pyramidal signs. Oral CoQ10 replacement causes dramatic improvement.^{113,114} The role of CoQ10 in pathogenesis of AOA1 is suspected in a family with a homozygous aprataxin gene mutation accompanied by presumed secondary CoQ10 deficiency and ataxia.¹¹⁵ Several gene mutations have been reported in CoQ10 deficiency, including *PDSS2* on chromosome 6 (COQ10D3), *PDSS1* on chromosome 10 (COQ10D2), *COQ2* on chromosome 4, *COQ4* on chromosome 9, *COQ6* on chromosome 14 (COQ10D6), *COQ8* on chromosome 1 (COQ10D4), and *COQ9* on chromosome 16 (COQ10D5).^{112,116}

Posterior Column Ataxia and Retinitis Pigmentosa—Posterior column ataxia and retinitis pigmentosa presents in childhood with visual field narrowing and proprioceptive

loss. By their 20s, patients are blind and have severe ataxia due to sensory loss, develop scoliosis, achalasia and weakness.¹¹⁷ Hyperintensities of the spinal cord are seen on MRI.¹¹⁸ The responsible gene is *FLVCR1* on chromosome 1,¹¹⁹ whose mutation causes mislocalization of the *FLVCR1* protein in cells and decreases its half-life.¹²⁰ Treatment is supportive.

Late-onset Tay Sachs disease (LOTSD)—Mutation of the *HEXA* gene on chromosome 15 leads to a deficiency of beta-hexosaminidase causing GM2-gangliosidosis,¹²¹ which affects the thalamus, brainstem, substantia nigra and cerebellum.¹²² The late-onset syndrome is characterized by areflexia, proximal muscle weakness, fasciculations, cerebellar ataxia, and psychiatric and behavioral problems. LOTSD is reported to have presented with FA phenotype.²⁴

Spinocerebellar ataxia, autosomal recessive (SCAR) 1-13—These are rare autosomal recessive ataxias, often reported in a single family. As gene loci become known, the disorders are named successively with the SCAR prefix. SCAR1 (AOA2), SCAR8 (SYNE1), and SCAR9 (COQ10D4) have already been discussed. Table 1 summarizes the major features of the SCARs.

Autosomal Dominant Ataxias

Autosomal dominant ataxias occur in every generation of a pedigree, with a 50% risk of inheritance of the mutation from the affected parent, and without a gender predilection. Depending on the disease course, autosomal dominant ataxias can be divided into the progressive, spinocerebellar ataxias (SCAs), and the episodic ataxias (EAs). Each entity in these categories is consecutively numbered to distinguish between various gene loci. SCA1 through SCA37 have been recognized and the list continues to grow. dentatorubral-pallidoluysian atrophy (DRPLA)¹²³ belongs to the SCA group despite the unique nomenclature. There have been excellent recent reviews of SCAs in the literature.¹²⁴⁻¹²⁷ Remarkably, SCA1-3, 6-8, 10, 12, 17, 31, 36 and dentatorubral-pallidoluysian atrophy (DRPLA) are caused by expanded microsatellite repeats. Of these, SCA1-3, 6, 7, 17 and DRPLA are caused by an expansion of polyglutamine-coding CAG repeats, while an expansion of non-coding repeats consisting of different repeat units causes SCA8 (CTG/CAG), 10 (ATTCT), 12 (CAG), 31 (TGGAA) and 36 (GGCCTG). Remaining SCAs are caused by point mutations. Table 2 highlights the major features of the SCAs along with their gene mutations and loci gleaned from a recent consensus statement about pathologic mechanisms of inherited ataxias.¹²⁷ It should be noted that there is no SCA9, as it was initially designated but not substantiated; mutations in the same gene are seen in SCA15 and SCA16; SCA19 and SCA22 are considered allelic disease; SCA24 is now assigned to a family of recessive ataxias (SCAR).

The EAs are characterized by transient reversible spells of ataxia, often associated with other features of variable duration.

Brief attacks (seconds to minutes) of ataxia associated with tremor and dysarthria with childhood onset is seen in EA1. Interictal myokymia can be seen clinically or detected

electrophysiologically. Some children have been reported with partial epilepsy, postural abnormalities, and tight heel cords.¹²⁸ Mutation of the potassium channel gene, *KCNA1*, on chromosome 12 is the culprit.

Longer episodes (lasting many hours) are seen in EA2, in association with nausea, vomiting, headache, dysarthria and diplopia.¹²⁸ Nystagmus and mild gait difficulty can be present interictally. EA2 is related to mutations in a calcium channel gene, *CACNA1A*, on chromosome 19 and is allelic to familial hemiplegic migraines and SCA6.

EA3 presents with short spells of ataxia and vertigo accompanied by tinnitus, and is localized to chromosome 1q42.¹²⁹ EA4, whose chromosomal localization has not been determined, begins later in life with episodes of ataxia and vertigo lasting many hours.¹³⁰ EA5 is phenotypically similar to EA1 and is related to a mutation in *CACNB4* gene on chromosome 2q23.¹³¹ Mutation in the *SLC1A3* gene on chromosome 5p13 is associated with EA6 which manifests with seizures, hemiplegia and episodes of ataxia lasting 2 to 3 hours.¹³² EA7 was reported in 7 members of a 4-generation family who experienced weakness, dysarthria and vertigo beginning in the second decade.¹³³

Gene tests for many of the dominant and recessive ataxias are available¹³⁴ (see GeneTests, www.genetests.org), including SCA1, 2, 3, 5, 6, 7, 10, 12, 13, 14, 17 and DRPLA. This list is likely to expand.

Other Inherited Ataxias

Mutations in the mitochondrial DNA (mtDNA) can cause progressive ataxia associated with myopathy, external ophthalmoplegia, endocrine deficiencies, short stature, and retinal pigmentary degeneration. Syndromes with ataxia associated with mitochondrial mutations include myoclonic epilepsy with ragged red fibers (MERRF), neuropathy, ataxia and retinitis pigmentosa (NARP), and less commonly, progressive external ophthalmoplegia, Kearns-Sayre syndrome, and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

Fragile X tremor-ataxia syndrome (FXTAS) is an X-linked disorder with ataxia described in the grandfathers of patients with fragile X mental retardation associated with mutation of the *FMR1* gene.¹³⁵ A full mutation has an expansion of over 200 CGG repeats, while normal chromosomes have fewer than 54 repeats. Other features of the syndrome include executive dysfunction, global brain atrophy, mild parkinsonism, dysautonomia, and psychiatric disturbances. Brain MRI classically shows T2 hyperintensity in the middle cerebellar peduncle and subcortical white-matter changes. Testing for a premutation in patients with ataxia, tremor, or both, and family history of mental retardation may be worthwhile.

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- Balance and coordination are products of complex circuitry involving the basal ganglia, cerebellum and cerebral cortex, as well as peripheral motor and sensory pathways.
- Malfunction of any part of this intricate circuitry can lead to imbalance and incoordination, or ataxia, of gait, the limbs or eyes, or a combination thereof.
- Ataxia can be a symptom of a multisystemic disorder, or it can manifest as the major component of a disease process.
- Ongoing discoveries of genetic abnormalities suggest the role of mitochondrial dysfunction, oxidative stress, abnormal mechanisms of DNA repair, possible protein misfolding, and abnormalities in cytoskeletal proteins.
- Few ataxias are fully treatable, and most are symptomatically managed.

Table 1

Spinocerebellar ataxia, autosomal recessive (SCAR)

	Other designations	Locus	Gene	Major features
SCAR1	AOA2, SCAN2	9q34.13	<i>SETX</i>	Ataxia, hyperkinesia, peripheral neuropathy and areflexia beginning in the second decade. Oculomotor apraxia in ~20%. Skeletal and foot deformities. Elevated α -fetoprotein, gamma-globulin, and creatine kinase levels in the serum.
SCAR2	Cerebelloparenchymal disorder III (Norman Type, CPD3), Cerebellar ataxia 1 (autosomal recessive; CLA1)	9q34-qter	<i>SCAR2</i>	Non-progressive cerebellar ataxia and cognitive impairment with severe granule cell loss beginning in childhood
SCAR3	Spinocerebellar ataxia with blindness and deafness (SCABD)	6p23-p21	<i>SCAR3</i>	Ataxia with blindness and deafness
SCAR4	Spinocerebellar ataxia with saccadic intrusions (SCASI); (Formerly SCA24)	1p36	<i>SCAS1</i>	Progressive ataxia with difficulty in reading, pyramidal signs, myoclonus, axonal neuropathy and <i>pes cavus</i> . Onset in 3 rd decade.
SCAR5	Cerebellar ataxia with mental retardation, optic atrophy and skin abnormalities (CAMOS)	15q25.3	<i>ZNF592</i>	Congenital spastic ataxia, developmental delay, microcephaly, optic atrophy, skin vessel changes and cerebellar atrophy.
SCAR6	Norwegian infantile onset ataxia	20q11-q13	<i>CLA3</i>	Infancy onset ataxia, hypotonia, mild spasticity, slow motor and speech development in early childhood, short stature and <i>pes cavus</i> .
SCAR7	Classic late-infantile neuronal ceroid lipofuscinosis 2 (CLN2) disease	11p15	<i>TPP1</i>	Slowly progressive ataxia in childhood with cerebellar atrophy and occasional pyramidal and posterior column signs.
SCAR8	Beauce ataxia, SYNE1 ataxia	6q25.1-q25.2	<i>SYNE1</i>	Pure cerebellar ataxia with occasional lower limb hyperreflexia beginning in middle age
SCAR9	COQ10D4, Coenzyme Q10 deficiency	1q42.13	<i>COQ8</i>	Ataxic form beginning in childhood with ataxia associated with pyramidal signs, mild cognitive decline and seizures. Muscle biopsy with ragged red fibers, and high lactic acid and CK levels. Other forms include myopathic, infantile, and Leigh syndrome.
SCAR10		3p22.1	<i>ANO10</i>	Cerebellar ataxia, LMN signs, and severe cerebellar atrophy beginning in the 3 rd decade
SCAR11		1q32.2	<i>SYT14</i>	Cerebellar ataxia with psychomotor retardation; onset in childhood
SCAR12	Spinocerebellar ataxia with mental retardation and epilepsy	16q21-q23	<i>SCAR12</i>	Childhood-onset cerebellar ataxia with generalized seizures, delayed psychomotor development and mild cerebellar atrophy.
SCAR13		6q24.3	<i>GRM1</i>	Infancy onset gait ataxia with delayed psychomotor development, profound mental retardation, poor speech, hyperreflexia, seizures, eye movement abnormalities, and cerebellar atrophy, ventriculomegaly on MRI
SCAR14	Infantile Onset Spinocerebellar Ataxia & Psychomotor Delay	11q13	<i>SPTBN2</i>	Non-progressive ataxia, psychomotor delay, tremor and UMN signs beginning in first year of life
SCAR15		3q29	<i>KIAA0226</i>	Slowly progressive cerebellar syndrome, generalized epilepsy starting in first year of life
SCAR16		16p13	<i>STUB1</i>	Variable age at onset with cerebellar syndrome; cognitive dysfunction, hypogonadism, spasticity, eye movement abnormalities in some patients.

Abbreviations: SCAR = spinocerebellar ataxia, autosomal recessive; CK = creatine kinase; LMN = lower motor neuron; UMN = upper motor neuron;

Table 2

Autosomal dominant Spinocerebellar ataxias (SCAs)

Name	Gene/protein	Locus	Mechanism	Major clinical features
SCA1	<i>ATXN1</i> /Ataxin-1	6p22	CAG repeat expansion; gain- and loss-of-function; transcription dysregulation; alteration of neuronal Ca channel signaling; poor degradation of and accumulation in Purkinje cells. [B]	Age of onset varies early-childhood to late-adulthood (mean age 30s). Cerebellar ataxia, dysarthria and UMN signs early. Later, dysphagia, ophthalmoparesis, sensory neuropathy, amyotrophy, slow saccades, cognitive decline. Chorea & dystonia possible. Diagnosis to death: 15-20 years. Anticipation is present.
SCA2	<i>ATXN2</i> /Ataxin-2	12q24	CAG repeat expansion; dysfunction of cellular RNA metabolism and endocytosis processes; possibly abnormal neuronal Ca channel signaling; [B60]	Similar to SCA1: very slow saccades, neuropathy, areflexia. Dystonia, dopa-responsive parkinsonism, myoclonus, tremor and cognitive decline possible. Infantile form reported. Association with ALS. Anticipation is present.
SCA3 (Machado-Joseph disease)	<i>ATXN3</i> /Ataxin-3	14q32	CAG repeat expansion; de-ubiquitination and dysfunctional interaction with transcriptional factors leading to destabilization and neuronal cell death	Most common SCA worldwide. SCA1-like phenotype: ataxia, brainstem signs (facial and tongue atrophy and fasciculations, dysphagia, poor cough), neuropathy, areflexia. Ophthalmoparesis, slow saccades, blepharospasm, eye-lid retraction, cognitive decline, sleep and autonomic disturbances possible. Dopa-responsive parkinsonism and dystonia may predominate. Anticipation is present.
SCA4		16q24	Unknown	Late adulthood onset ataxia and sensory axonal motor neuropathy
SCA5 (Lincoln ataxia)	<i>SPTBN2</i> /β-IM Spectrin	11q13	Defect in neuronal membrane skeleton;	Slowly progressive, early-onset bulbar signs and cerebellar syndrome
SCA6	<i>CACNA1A</i>	19p13	CAG repeat expansion; cytoplasmic aggregations of the alpha-1A calcium channel protein;	Late adulthood onset cerebellar syndrome with saccadic abnormalities and nystagmus. Anticipation is present.
SCA7	<i>ATXN7</i> /Ataxin-7	3p14	CAG repeat expansion; Transcription dysregulation;	Onset during first decade, Huntington disease-like phenotype with deafness and pigmentary retinopathy. Prominent anticipation is present.
SCA8	<i>ATXN8OS</i> / <i>ATXN8</i> /Ataxin-8	13q21	RNA gain-of-function; Repeat Associated Non-ATG (RAN) translation	Cerebellar syndrome with sensory neuropathy, spasticity, cognitive and psychiatric abnormalities. Reduced penetrance.
SCA10	<i>ATXN10</i> /Ataxin-10	22q13	ATTCT repeat expansion; gain-of-function causing RNA toxicity	Cerebellar syndrome with epilepsy. Anticipation is present.
SCA11	<i>TTBK2</i> /Tau tubulin kinase 2	15q15	Tau phosphorylation dysregulation	Cerebellar syndrome with hyperreflexia
SCA12	<i>PPP2R2B</i> /Protein phosphatase 2A	5q32	CAG repeat expansion; protein phosphatase (PP2A) and transcription regulation	Cerebellar syndrome including upper extremity tremor, hyperreflexia, axonal neuropathy, cognitive decline. Atrophy of cerebral cortex and cerebellum. Anticipation is present.
SCA13	<i>KCNC3</i> /KCNC3	19q13	Potassium channel dysfunction;	Variable phenotype depending on the mutation. Early onset

Name	Gene/protein	Locus	Mechanism	Major clinical features
				cerebellar syndrome with cognitive dysfunction vs. later onset cerebellar ataxia with normal ocular movements.
SCA14	<i>PRKCG</i> /Protein kinase C-gamma	19q13	Alterations of neuronal Ca channel signaling, synaptic transmission, proteasome degradation and neurites;	Cerebellar syndrome, myoclonus in early-onset, dystonia and cognitive decline in some.
SCA15	<i>ITPR1</i> /ITPR1	3p26	insufficiency in the smooth endoplasmic reticulum calcium	Slowly progressive cerebellar syndrome
			channel IP3R1	
SCA16	<i>ITPR1</i> /ITPR1	3p26	insufficiency in the smooth endoplasmic reticulum calcium channel IP3R1	Slowly progressive cerebellar syndrome with head tremor
SCA17 (HDL4)	<i>TBP</i> /TATA binding protein	6q27	CAG repeat expansion; Transcription dysregulation; reduced levels of chaperones	Cerebellar syndrome with UMN signs, extrapyramidal signs, epilepsy. Occasional hypogonadism. Anticipation is present.
SCA18	Unknown	7q22-q32	Unknown	Cerebellar syndrome with sensory neuropathy, muscle weakness and atrophy. Occasional deafness.
SCA19	<i>KCND3</i> /KCND3	1p21-q21	Potassium channel dysfunction;	Cerebellar syndrome with variable reflexes, myoclonus, tremor. Occasional deafness, spasticity
SCA20		11q12	Chromosomal duplication;	Ataxia, dysphonia, palatal tremor. Dentate calcifications on imaging.
SCA21		7p21	Unknown	Slowly progressive cerebellar syndrome, hyperreflexia, parkinsonism unresponsive to L-dopa.
SCA22	<i>KCND3</i> /KCND3	1p21	Potassium channel dysfunction;	Slowly progressive gait ataxia and nystagmus. Anticipation is reported.
SCA23	<i>PDYN</i> /Prodynorphin	20p13	Upregulation of dynorphin A leading to cerebellar toxicity;	Ataxia with sensory loss and pyramidal signs.
SCA24				(now called SCAR4)
SCA25	Unknown	2p21-p15	Unknown	Cerebellar syndrome with sensory neuropathy and gastrointestinal features. Severe cerebellar atrophy.
SCA26	<i>EEF2</i> /EEF2	19p13	RNA metabolism, proteostatic disruption;	Slowly progressive cerebellar syndrome
SCA27	<i>FGF14</i> /Fibroblast growth factor 14	13q33	Signal transduction; dysregulation of sodium channels;	Cerebellar syndrome with psychiatric features, tremor, dyskinesia.
SCA28	<i>AFG3L2</i> /AFG3L2	18p11	Mitochondrial membrane protease dysfunction	Cerebellar syndrome with ophthalmoparesis and UMN signs. Myoclonic epilepsy rare.
SCA29	<i>ITPR1</i> /ITPR1	3p26	Unknown	Congenital, non-progressive, variant of SCA15.
SCA30	Unknown	4q34	Unknown	Slowly progressive, late-onset cerebellar syndrome
SCA31	<i>BEAN</i> /BEAN	16q21	TGGAA repeat expansion; unknown mechanism but RNA toxicity is suspected	Late-adulthood onset.

Name	Gene/protein	Locus	Mechanism	Major clinical features
SCA32	Unknown	7q32	Unknown	Cerebellar syndrome with azospermia and cognitive impairment.
SCA34	Unknown	6p12	Unknown	Skin lesions soon after birth resolving by adulthood when ataxia, dysarthria, nystagmus, and areflexia appear. Cognition and sensation unaffected.
SCA35	<i>TGM6</i> / Transglutaminase 6	20p13	Impaired cross-linking of proteins	Cerebellar syndrome with UMN signs, sensory loss, and spasmodic torticollis.
SCA36	NOP56/NOP56 ribonucleoprotein	20p13	GGCCTG repeat expansion; toxic RNA gain of function;	Slowly progressive, late-onset cerebellar syndrome, UMN and LMN signs.
SCA37	Unknown	1p32	Unknown	Slowly progressive, late-onset cerebellar syndrome with abnormal vertical eye movements.

Abbreviations: ALS = amyotrophic lateral sclerosis, SCA = spinocerebellar ataxia, UMN = upper motor neuron, LMN = lower motor neuron