Chapter 16: Ataxia & Cerebellar Disease

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INTRODUCTION

Ataxia (from the Greek "without order") denotes incoordination and imbalance, involving limbs, stance, and gait, as well as speech and ocular disturbances. In practice, the term is used when these symptoms arise from neurologic dysfunction involving the cerebellum and its connecting pathways. However, ataxia can also result from malfunction of sensory input from proprioceptive sensory pathways or the vestibular system into the cerebellum. Ataxia often results in significant loss of independence, and injuries from falls as well as other complications lead to considerable morbidity.

APPROACH TO THE ATAXIC PATIENT

Once ataxic features of coordination or gait are recognized, cerebellar ataxia needs to be distinguished from so-called "*sensory ataxia*" resulting from proprioceptive abnormalities, and from labyrinthine ataxia seen with vestibular disorders. With proprioceptive ataxia, incoordination often increases dramatically when the patient's eyes are closed. Oculomotor symptoms such as nystagmus point away from sensory ataxia. Patients with labyrinthine ataxia also have impaired gait and balance, but speech is not affected and limb movements are coordinated. Myelopathy, basal ganglia disease, or bihemispheric disease can also cause incoordination and gait dysfunction. It is therefore important in assessing ataxia to make sure that the clumsiness observed is independent of isometric strength, muscle tone, reflex abnormalities, and problems with spatial planning. In practice, however, the clinical picture may be complicated by coexistence of these abnormalities with cerebellar disease.

Because ataxia may result from acquired disorders or be genetically determined (Table 16–1), a careful family history is necessary. The time course of disease, age of onset, additional symptoms such as spasticity or cognitive dysfunction, and evidence of systemic disease help refine diagnostic possibilities.

Table 16–1.

Causes of ataxia: categories of diseases affecting the cerebellum and time course of disease.

Category	Disease	Time Course[a]		
		Acute	*Subacute*	*Chronic*
Developmental	Arnold-Chiari malformation, Dandy-Walker malformation, cerebellar hypoplasia	–	–	+
Hereditary	Autosomal-dominant spinocerebellar ataxias (see Tables 16–6 and 16–7)	–	–	+
	Autosomal-recessive spinocerebellar ataxias—Friedreich ataxia, others (see Table 16–9)	–	–	+
	Fragile X-associated tremor and ataxia syndrome	–	–	+
	Episodic ataxias (see Table 16–8)	+	–	(+)
	Mitochondrial disorders (see Table 16–10)	+	+	+

	Leukodystrophies, storage disorders	–	–	+
	Urea cycle disorders	+	+	+
Vascular	Ischemic cerebellar stroke (see Table 16–4), ataxic hemiparesis, lacunar stroke syndrome	+	–	–
	Cerebellar hemorrhage	+	–	–
	Arteriovenous malformations	+	+	+
	Cavernous malformations	+	–	–
Toxin-associated	Alcohol	+	+	+
	Metals (lead, thallium, mercury)	+	+	+
	Solvents	+	–	+
Medication-associated	Anticonvulsants (phenytoin, carbamazepine), amiodarone, cytotoxic drugs (methotrexate, cisplatin)	+	+	+
Neoplastic	Metastatic tumors (lung, breast, melanoma, renal, seminoma, teratoma)	–	+	+
	Medulloblastoma, glioma, oligodendroglioma, astrocytoma, meningioma, ependymomas, cerebellopontine tumors	–	+	+
	Cerebellar hemangioblastoma (von Hippel-Lindau syndrome)	–	+	+
Infectious	Abscess (bacterial, fungal)	–	+	+
	Acute viral cerebellitis (EBV, HHV-6, HSV-1, mumps)	+	–	–
	HIV encephalitis	–	(+)	+
	Prion disease	–	(+)	+
	Encephalitic bacterial infection, including listeriosis	+	(+)	–
Immune-associated	Multiple sclerosis	+	+	+
	Postinfectious cerebellitis	+	(+)	–
	Gluten ataxia	–	+	+
	Paraneoplastic (see Table 16–5)	–	+	+
Metabolic or nutritional	Hypothyroidism, hypoglycemia	–	(+)	+
	Deficiency in vitamins B_1, B_{12}, or E	–	–	+

EBV = Epstein-Barr virus; HHV-6 = human herpesvirus 6; HSV-1 = herpes simplex virus 1; +, present; –, absent.

[a]Parentheses signify a less likely, although possible, time course for that process.

Clinical Findings & Their Relation to Cerebellar Anatomy

The close spatial and functional association of cerebellum with the brainstem explains why cerebellar symptoms can originate in the brainstem itself. Additionally, space occupying cerebellar lesions may rapidly lead to compression of the brainstem. The cerebellum can be functionally divided into three regions—anterior lobe and rostral vermis, flocculonodular and posterior lobes, and cerebellar hemispheres—corresponding to characteristic clinical syndromes (Table 16–2). Clinical features of cerebellar disease are described in Table 16–3.

Table 16–2.

Cerebellar syndromes: functional anatomy and clinical findings.

Cerebellar Syndrome	Anatomic Location	Clinical Findings
Rostral vermis syndrome	Anterior lobe, rostral vermis	Wide-based stance and gait with proportionally less appendicular ataxia Infrequent presence of hypotonia, nystagmus, dysarthria
Caudal vermis syndrome	Flocculonodular and posterior lobes	Axial disequilibrium (trunk and head ataxia) but proportionally little or no appendicular ataxia Staggering gait Occasionally spontaneous nystagmus and rotated postures of head Vertigo Downbeat or gaze-evoked nystagmus, or both Impaired smooth pursuit
Cerebellar hemispheric syndrome	Cerebellar hemispheres	Ipsilateral appendicular (limb) ataxia with dysmetria, dysdiadochokinesia (arms > legs) Kinetic (intention) and statis tremors Dysarthria Muscle hypotonia (acute only) Excessive rebound Ocular dysmetria

Table 16–3.

Clinical signs of cerebellar disease.

Sign	Definition
Truncal ataxia	Oscillations while sitting or standing; falling may occur toward the side of a unilateral lesion
Wide-based stance or gait	Feet placed widely apart; difficulty standing with feet together or walking tandem in heel-to-toe test
Dysdiadochokinesis	Impaired rapid alternating movements, tested by alternating supination-pronation of hands or by toe-tapping
Dysmetria	Errors in judging distance with body movements, tested by finger-to-nose test, which may result in underestimation (hypometria) or overestimation with transient overshoot (hypermetria)
Impaired check	Failure to arrest a limb movement, tested by flexing the arm at the elbow against resistance that is suddenly released
Past pointing	Termination of a movement, briefly, away from the target, tested by extending the arm in front, raising it, and attempting to return it to the identical position with eyes closed
Hypotonia	Decreased muscle tone
Dysarthria	Unclear pronunciation with normal language content and meaning
Scanning speech	Abnormally long pauses between words or syllables
Kinetic tremor	Tremor that occurs with voluntary movement, with worsening on target approach; also called *intention tremor*
Postural tremor	Tremor that persists once a target is reached, easily elicited by stretching arms out with palms facing down
Nystagmus	Inability to maintain gaze fixation, with slow phase followed by rapid saccadic correction, commonly gaze evoked but also in a primary position; may be downbeat, upbeat, or horizontal
Dysmetric saccades	Analogous to limb dysmetria, resulting in hypermetria or hypometria on saccade to a target presented by the examiner

Therapeutic Approaches in Cerebellar Disease

Particularly in patients with chronic ataxia, a multidisciplinary approach involving physicians, psychologists, therapists, nursing specialists, and social work services helps address diverse issues, including optimizing physical function, managing long-term disability, and social and psychological issues affecting both patient and caregivers. Genetic testing is best done in the context of rigorous and careful counseling. Some patients may wish to participate in trials offered at centers specializing in movement disorders. The National Ataxia Foundation is an excellent source of information and can be found at http://www.ataxia.org.

A. Physical and Occupational Therapy

Added weight can help tremor and may also benefit limb ataxia, but at greater weight loads, performance tends to decline. Adaptive devices that incorporate damping mechanisms are available. Physical therapy is helpful for many patients who manifest generalized deconditioning, weakness, or spasticity. Various therapeutic modalities such as cycling, home balance programs, and video game–based therapies are being investigated, with small studies suggesting benefit. Gait adaptability training, focusing on object avoidance has also been shown in a small study to benefit those with

cerebellar degeneration. The greatest obstacles limiting efficacy of physical therapy are lack of sufficient therapists who understand ataxia, lack of clinically determined effective protocols for physical therapy, and the need for continuous therapy to ensure the gains are not lost over time after cessation of therapy.

Chang YJ, et al. Cycling regimen induces spinal circuitry plasticity and improves leg muscle coordination in individuals with spinocerebellar ataxia. *Arch Phys Med Rehabil* 2015;96:1006–1013.
[PubMed: 25668777]

Fonteyn EM, Heeren A, Engels JJ, Boer JJ, van de Warrenburg BP. Gait adaptability training improves obstacle avoidance and dynamic stability in patients with cerebellar degeneration. *Gait Posture* 2014;40:247–251.
[PubMed: 24786476]

Fonteyn EM, et al. The effectiveness of allied health care in patients with ataxia: A systematic review. *J Neurol* 2014;261:251–258.
[PubMed: 23589192]

Keller JL, Bastian AJ. A home balance exercise program improves walking in people with cerebellar ataxia. *Neurorehabil Neural Repair* 2014;28:770–778.
[PubMed: 24526707]

Ilg W, et al. Video game-based coordinative training improves ataxia in children with degenerative ataxia. *Neurology* 2012;79:2056–2060.
[PubMed: 23115212]

B. Speech and Swallowing Therapy

Patients who suffer from dysarthria often benefit from speech therapy. Many require formal swallowing evaluations, and exercises as well as dietary modification may help those with dysphagia, an important cause of morbidity. In advanced cases, feeding via a percutaneous endoscopic gastrostomy tube can reduce risk of aspiration.

C. Pharmacotherapy

There has been little success in treating ataxia with medications. Action tremor may respond to primidone, β-adrenergic blocking agents such as propranolol, and benzodiazepines. Appropriate medications may be given for associated symptoms such as spasticity, parkinsonism, dystonia, bladder dysfunction, and orthostatic hypotension.

D. Surgical Treatment

High-frequency electrical stimulation of the ventral intermediate nucleus of the thalamus, or surgical lesions, can reduce cerebellar tremor. There is, however, no effect on ataxia. Transcranial magnetic stimulation and direct current stimulation are undergoing clinical testing for their potential to improve symptoms.

Celnik P. Understanding and modulating motor learning with cerebellar stimulation. *Cerebellum* 2015;14:171–174.
[PubMed: 25283180]

E. Gene and Stem Cell Therapy

Recent advances have enhanced our understanding of the genetic basis of many of the inherited ataxias, and the possibility of gene therapy is being studied in other neurodegenerative diseases. Currently there are no such therapies for ataxia. Animal models using mesenchymal stem cells are showing promise in reducing peripheral nervous system damage in specific ataxic disorders such as spinocerebellar ataxia 1. However, as yet there is no evidence for their use in the clinic.

Mieda T, et al. Mesenchymal stem cells attenuate peripheral neuronal degeneration in spinocerebellar ataxia type 1 knockin mice. *J Neurosci Res* 2016;94:246–252.
[PubMed: 26707550]

Trujillo-Martin MM, et al. Effectiveness and safety of treatments for degenerative ataxias: A systematic review. *Mov Disord* 2009;24:1111–1124.
[PubMed: 19412936]

ACQUIRED ATAXIAS

CEREBELLAR ISCHEMIC STROKE SYNDROMES

ESSENTIALS OF DIAGNOSIS

- Acute onset of ataxia with other signs and symptoms
- Magnetic resonance imaging (MRI) of the brain, showing hyperintensity on diffusion-weighted images initially and on fluid-attenuated inversion recovery and T2-weighted sequences later

General Considerations

Approximately 2% of all ischemic strokes and 10% of all intracerebral hemorrhages affect the cerebellum. Patients with cerebellar infarction often have brainstem signs because of common arterial supplies. The vessel most frequently implicated is the posterior inferior cerebellar artery, but infarctions also occur in the territories of the superior cerebellar artery and the anterior inferior cerebellar artery (see Chapter 10). Ataxia may also arise as a result of lacunar infarction, most commonly as the ataxic-hemiparesis syndrome.

Clinical Findings

A. Symptoms and Signs

Symptoms and signs of cerebellar infarction are summarized in Table 16–4. Large cerebellar infarctions often cause headaches.

Table 16–4.

Clinical findings in infarction of the posterior inferior, superior, and anterior inferior cerebellar arteries.

Symptom	PICA	SCA	AICA
Vertigo, nausea, vomiting	+	+	+
Nystagmus	+	+	+
Dysarthria	+	+	+
Ipsilateral Horner syndrome	+	+	+
Contralateral trochlear nerve palsy	–	+	–
Ipsilateral facial palsy	–	–	+
Ipsilateral facial hypalgesia and thermoanesthesia	+	–	+
Ipsilateral facial hypesthesia	–	–	+
Contralateral facial hypalgesia and thermoanesthesia	–	+	–
Ipsilateral hearing impairment or loss	–	+	+
Ipsilateral palatal, pharyngeal, and vocal cord paralysis	+	–	–
Contralateral trunk and limb hypalgesia and thermoanesthesia	+	+	+
Ipsilateral truncal lateropulsion	+	+	–
Ipsilateral appendicular ataxia	+	+	+

AICA = anterior inferior cerebellar artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery; +, present; –, absent.

B. Laboratory Findings

There may be evidence of unrecognized risk factors such as diabetes or hypertension. Other tests for ischemic stroke are discussed in Chapter 10.

C. Imaging Studies

Computed tomography (CT) of the head is performed acutely to rule out hemorrhage. MRI of the brain with diffusion-weighted imaging can establish the clinical diagnosis acutely. Magnetic resonance angiography or vascular ultrasound can assess the extent of atherosclerotic disease in the basilar and vertebral arteries. In selected patients with recent whiplash or other trauma, vertebral artery dissection can be identified by MRI, CT angiography, or cerebral angiography.

Treatment & Complications

Therapy follows general recommendations for any patient with ischemic stroke (see Chapter 10). However, cerebellar infarcts that are more than 2.5 cm in diameter must be intensively monitored because of the risk of edema leading to brainstem compression or obstructive hydrocephalus and coma

2–4 days after stroke onset. Surgical intervention may be required.

CEREBELLAR HEMORRHAGE

ESSENTIALS OF DIAGNOSIS

- Sudden onset of ataxia, possible headache
- Hemorrhage detected by CT scan of the head

General Considerations

The most frequent causes of cerebellar hemorrhage are hypertension and vascular malformations.

Clinical Findings

A. Symptoms and Signs

Patients characteristically present with sudden onset of headache and inability to stand or walk. Ipsilateral limb ataxia is often present, and some patients have ipsilateral gaze or abducens paresis. Hemiparesis and long-tract sensory signs are usually conspicuously absent.

B. Laboratory and Imaging Findings

CT or MRI scan of the head demonstrates hemorrhage, and there may be surrounding signal abnormality as a result of edema. Evidence of herniation of the foramen magnum may be present. Laboratory tests should include coagulation studies.

C. Special Tests

MRI may identify an underlying vascular malformation, but if imaging findings are negative and such a lesion is suspected, cerebral angiography may be undertaken.

Treatment

Cerebellar hemorrhages more than 3 cm in diameter require emergency surgical evacuation, even in patients seemingly stable with full alertness. Deterioration, when it occurs, can be abrupt and fatal. Medical treatment of smaller cerebellar hemorrhages follows the general recommendations for treatment of intracranial hemorrhage (see Chapter 11).

Rincon F, Mayer SA. Clinical review. Critical care management of spontaneous intracerebral hemorrhage. *Crit Care* 2008;12:237. [PubMed: 19108704]

TOXINS & NUTRITIONAL DEFICIENCIES

1. Ethanol

Cerebellar ataxia in alcoholic individuals can be the result of acute intoxication, Wernicke-Korsakoff disease, or alcoholic cerebellar degeneration. These disorders are discussed in Chapter 33.

2. Solvents

ESSENTIALS OF DIAGNOSIS

- Usually sudden onset
- History of solvent abuse
- Associated findings include behavioral changes

Acutely, ataxia as well as other neurologic symptoms may accompany intoxication by inhalants (see Chapter 34). Most often, effects are short-lived and the ataxia needs no specific treatment, but other complications, including cardiac arrhythmia, can be fatal. Chronic toluene exposure has been linked to encephalopathy and ataxia, with brainstem and cerebellar white matter changes.

Uchino A, et al. Comparison between patient characteristics and cranial MR findings in chronic thinner intoxication. *Eur Radiol* 2002;12:1338–1341. [PubMed: 12042936]

3. Medications and Illicit Drugs Associated With Ataxia

Barbiturates, benzodiazepines, and many anticonvulsants, most notably phenytoin and carbamazepine, may all lead to dysarthria and ataxia. Chemotherapeutic agents including 5-fluorouracil, methotrexate, cyclosporine, and cytosine arabinoside are also associated with ataxia, as is lithium carbonate. A case of tacrolimus-induced subacute cerebellar ataxia without supratentorial involvement demonstrated partial improvement with withdrawal of the medication. Amiodarone, procainamide, and bismuth salts are other therapeutic agents that can cause ataxia.

Kaleyias J, Faerber E, Kothare SV. Tacrolimus induced subacute cerebellar ataxia. *Eur J Paediatr Neurol* 2006;10:86–89. [PubMed: 16530436]

4. Heavy Metal Intoxication

Heavy metals, including mercury, lead, and thallium may cause ataxia, in addition to other symptoms.

5. Nutritional Deficiencies

Deficiency in cobalamin (vitamin B_{12}), although typically recognized as a cause of dementia and myelopathy, may rarely give rise to isolated cerebellar ataxia. Deficiency of vitamin B_1, vitamin E, thiamine, and possibly zinc can produce cerebellar signs and symptoms.

Morita S, et al. Cerebellar ataxia and leukoencephalopathy associated with cobalamin deficiency. *J Neurol Sci* 2003;216:183–184. [PubMed: 14607321]

ABNORMAL HOMEOSTASIS & ATAXIA

Carbon monoxide poisoning resulting in reduced oxygenation can lead to cerebellar damage, because Purkinje cells are susceptible to anoxic injury. Hyperthermia from heat exposure or medications resulting in, for example, neuroleptic malignant syndrome may cause encephalopathy with ataxia as a clinical feature. Loss of Purkinje cells and cerebellar efferent pathways have been noted in those suffering from severe pyrexia.

Alekseeva N, et al. Toxic-metabolic, nutritional, and medicinal-induced disorders of cerebellum. *Neurol Clin* 2014;32:901–911. [PubMed: 25439288]

ENDOCRINE DISEASE & ATAXIA

Cerebellar dysfunction may be the result of hypothyroidism, hypoparathyroidism, or hypoglycemia. These disorders are discussed in Chapter 32.

CEREBELLAR NEOPLASMS

In children, tumors causing ataxic syndromes include medulloblastoma, cerebellar astrocytoma, and ependymoma. In adults, metastatic tumors and hemangioblastoma are the commonest cerebellar neoplasms. For further discussion, see Chapter 12.

INFECTIOUS CAUSES OF ATAXIA

Several infectious agents produce cerebellar mass lesions such as abscess, tuberculoma, or toxoplasmoma. In children (less often in adults), ataxia with explosive onset is the initial manifestation of encephalitis affecting predominantly the posterior fossa; agents include *Haemophilus influenzae*, rubella, and other viruses. Postinfectious ataxia may follow infection by varicella, although there is often only a vague viral prodrome. Postinfectious cerebellitis can be prolonged, and reports of improvement in isolated cases encourage the use of intravenous immunoglobulins when symptoms are protracted and debilitating. Ataxia is often a feature of sporadic Creutzfeldt-Jakob disease, which is characterized by rapidly progressive dementia and accompanied by myoclonus; 90% of affected patients die within 12 months. Ataxia has also been associated with other prion diseases, notably Gerstmann-Sträussler-Scheinker disease (see Chapter 29). Ataxia may result from cerebellar complications of HIV, usually from opportunistic infection, vasculitis, or malignancy (see Chapter 28). Rarely, cerebellar ataxia occurs in the absence of these processes, perhaps as a direct consequence of HIV infection. A large case series from Sweden has demonstrated the presence of Epstein-Barr virus in the cerebellum as another infectious cause of cerebellar disease.

Collins SJ, et al. Transmissible spongiform encephalopathies. *Lancet* 2004;363:51–61.
[PubMed: 14723996] (Reviews the clinical spectrum, epidemiology, and molecular biology of prion diseases in general, including those associated with cerebellar ataxia.)

Cooper SA, et al. Sporadic Creutzfeldt-Jakob disease with cerebellar ataxia at onset in the UK. *J Neurol Neurosurg Psychiatry* 2006;77:1273–1275.
[PubMed: 16835290]

Gruis KL, et al. Cerebellitis in an adult with abnormal magnetic resonance imaging findings prior to the onset of ataxia. *Arch Neurol* 2003;60:877–880.
[PubMed: 12810494]

Kwakwa HA, Ghobrial MW. Primary cerebellar degeneration and HIV. *Arch Intern Med* 2001;161:1555–1556.
[PubMed: 11427105]

Millichap JG. Epstein-Barr virus neurologic complications. *Pediatr Neurol Brief* 2015;29:88.
[PubMed: 26933545]

Narang HK. A critical review of atypical cerebellum-type Creutzfeldt-Jakob disease: Its relationship to “new variant” CJD and bovine spongiform encephalopathy. *Exp Biol Med (Maywood)* 2001;226:629–639.
[PubMed: 11444099]

Schmahmann JD. Plasmapheresis improves outcome in postinfectious cerebellitis induced by Epstein-Barr virus. *Neurology* 2004;62:1443.
[PubMed: 15111700]

Tagliati M, et al. Cerebellar degeneration associated with human immunodeficiency virus infection. *Neurology* 1998;50:244–251.
[PubMed: 9443487] (First report of primary cerebellar degeneration in association with HIV, in 10 patients presenting with gait ataxia and dysarthria.)

ATAXIA ASSOCIATED WITH INFLAMMATORY & AUTOIMMUNE DISEASE

Ataxia is a common manifestation of multiple sclerosis, occurring subacutely, chronically, or, less often, acutely (see Chapter 17). A few cases of cerebellar ataxia have been reported in patients with Hashimoto disease, in association with elevated titers of antithyroglobulin antibody and antithyroperoxidase antibody. Patients can develop ataxia in the euthyroid state. The significance of this association to Hashimoto encephalopathy is unclear. High titers of anti–glutamic acid decarboxylase (GAD) antibodies have also been associated with some cases of cerebellar ataxia, and this may occur together with type 1 diabetes. Primary autoimmune cerebellar ataxia, for which there is no known trigger, has been described in individuals older than 50 years, and it has a slow course. However, further study is required to understand its etiology, pathology, and clinical spectrum.

Bayreuther C, et al. Auto-immune cerebellar ataxia with anti-GAD antibodies accompanied by de novo late-onset type 1 diabetes. *Diabetes Metab* 2008;34:386–388.
[PubMed: 18583169]

Mitoma H, et al. Consensus paper: Neuroimmune mechanisms of cerebellar ataxias. *Cerebellum* 2016;15:213–232.
[PubMed: 25823827]

Selim M, Drachman DA. Ataxia associated with Hashimoto's disease: Progressive non-familial adult onset cerebellar degeneration with autoimmune thyroiditis. *J Neurol Neurosurg Psychiatry* 2001;71:81.
[PubMed: 11413268]

GLUTEN ATAXIA

ESSENTIALS OF DIAGNOSIS

- Chronic, progressive ataxia, sometimes with myoclonus
- Clinical features of celiac disease, including characteristic biopsy findings
- Associated antibodies—antigliadin immunoglobulins G (IgG) and A (IgA), antiendomysial, and antitransglutaminase antibodies

General Considerations

Celiac disease is an immune-mediated gluten-sensitive enteropathy, with small bowel villous atrophy demonstrated on biopsy. Clinical improvement follows adherence to a gluten-free diet. The disease affects nearly 1% of the population. Neurologic syndromes, including ataxia, occur in 6–10% of such patients. In a large series of more than 1000 patients with progressive cerebellar ataxia in England, gluten ataxia had a prevalence of 15% among all ataxias, and 41% among idiopathic sporadic ataxias. Cerebellar atrophy and Purkinje cell loss have sometimes been observed at postmortem examination. The nature of this association, and the significance of serologic findings, including increased antigliadin antibody titers, which are produced in response to prolamin in wheat, is not yet fully understood.

Clinical Findings

A. Symptoms and Signs

Patients have progressive gait and limb ataxia, and sometimes dysarthria, abnormal eye movements, pyramidal signs, and memory decline. Some have myoclonus and palatal tremor. The disorder typically affects individuals older than 50 years of age but cases in younger people, including pediatric patients, have been reported. Gastrointestinal complaints may be present or absent. Associated conditions sometimes include osteoporosis, dermatitis herpetiformis, autoimmune thyroiditis, and diabetes mellitus. There is increased risk of lymphoma.

B. Laboratory Findings

There are elevations in antigliadin (IgA and IgG), antiendomysial (IgA), or antitransglutaminase (IgA) antibody titers. Anti-GAD autoantibodies and antiganglioside antibodies have also been detected. There may be vitamin deficiency, including folate, vitamin K, and vitamin D; iron-deficiency anemia; and elevated liver enzymes. The use of new, specific serologic markers such as anti-TG6 antibodies may aid in accurately diagnosing this condition, but these antibodies are not yet readily available for clinical testing.

C. Imaging Studies

MRI often reveals cerebellar atrophy, sometimes limited to the vermis and sometimes pancerebellar. Of note. magnetic resonance spectroscopy shows a reduced *N*-acetylaspartate/creatinine ratio in the vermis, which may be present in even newly diagnosed cases of gastrointestinal celiac disease, suggesting early cerebellar dysfunction.

Treatment

Improvement sometimes follows implementation of a gluten-free diet. Intravenous immunoglobulin treatment, as well as mycophenolate mofetil, cyclosporine, or cyclophosphamide, has been reported to help in a small number of patients.

Hadjivassiliou M, et al. Gluten ataxia. *Cerebellum* 2008;7:494–498.
[PubMed: 18787912]

Mitoma H, et al. Consensus paper: Neuroimmune mechanisms of cerebellar ataxias. *Cerebellum* 2016;15:213–232.
[PubMed: 25823827]

Mitoma H, Hadjivassiliou M, Honnorat J. Guidelines for treatment of immune-mediated cerebellar ataxias. *Cerebellum Ataxias* 2015;10:14.
[PubMed: 26561527]

Souyah N, et al. Effect of intravenous immunoglobulin on cerebellar ataxia and neuropathic pain associated with celiac disease. *Eur J Neurol* 2008;15:1300–1303.
[PubMed: 19049545]

ATAXIA OF PARANEOPLASTIC ORIGIN

ESSENTIALS OF DIAGNOSIS

- Acute or subacute onset of ataxia
- Underlying neoplasm is often unrecognized
- Antibodies specifically associated with some paraneoplastic syndromes

Paraneoplastic syndromes are discussed in Chapter 13. Syndromes that include cerebellar ataxia are summarized in Table 16–5.

Table 16–5.

Paraneoplastic syndromes producing ataxia and cerebellar degeneration.

Antibody	Neurologic Findings	Associated Cancer	Commercial Test Available
Anti-Hu (ANNA-1)	PCD, sensory neuronopathy, encephalomyelitis	SCLC, prostate, neuroblastoma	+
Anti-Yo (PCA-1)	PCD	Breast, ovary, lung	+
Anti-Ri (ANNA-2)	PCD, opsoclonus-myoclonus	Breast, lung, gynecologic, bladder	+
Anti-Ma1	PCD, brainstem encephalitis	Lung, other	+
CV2	PCD, encephalomyelitis, chorea, neuropathy	SCLC, thymoma	+
Anti-metabotropic glutamate receptor R1	PCD	Hodgkin disease	–
Anti-Tr (atypical cytoplasmic antibody, PCA-Tr)	PCD	Hodgkin disease	–
Anti-PCA-2	PCD, encephalomyelitis, Lambert-Eaton syndrome	SCLC	–
Anti-Zic 4	PCD, encephalitis	SCLC	+
Anti-Homer3	Dysarthria, nystagmus, limb and ataxia, vertigo, vomiting	Lung	–
Anti-Sj/ITPR1	Cerebellar ataxia—can be progressive	NSCLC, breast, melanoma	–
Anti-CARPIII	Dysarthria, intention tremor, limb and gait ataxia, vertigo, horizontal or vertical nystagmus	Melanoma, ovarian cystadenocarcinoma	–
Anti-PKCγ	PCD	NSCLC Papillary adenocarcinoma of liver	–
Anti-Ca/AHRGAP26	Cerebellar ataxia, vomiting, cognitive decline	Ovarian	–
Anti-VGCC	PCD, Lambert-Eaton syndrome	SCLC, small-cell prostate cancer, non-Hodgkin lymphoma	+
Anti-NB/AP3B2	Progressive subacute cerebellar ataxia, hyperreflexia	Not yet identified	–
Anti-ampiphysin	PCD, Stiff-Person syndrome	Breast	+
Anti-GAD	PCD, Stiff-Person syndrome	Hepatocellular carcinoma	+

PCD = Paraneoplastic cerebellar degeneration; SCLC = Small cell lung carcinoma; NSCLC = non-small cell lung carcinoma; +, available; −, not available

Jarius S, Wildermann B: 'Medusa-head ataxia': The expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 1: Anti-

mGluR1, anti-Homer-3, anti-Sj/ITPR1 and anti-CARP VIII. *J Neuroinflammation* 2015;12:166.
[PubMed: 26377085]

Jarius S, Wildermann B: 'Medusa head ataxia': The expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 2: Anti-PKC-gamma, anti-GluR-delta2, anti-Ca/ARHGAP26 and anti-VGCC. *J Neuroinflammation* 2015;12:167.
[PubMed: 26377184]

Jarius S, Wildermann B: 'Medusa head ataxia': The expanding spectrum of Purkinje cell antibodies in autoimmune cerebellar ataxia. Part 3: Anti-Yo/CDR2, anti-Nb/AP3B2, PCA-2, anti-Tr/DNER, other antibodies, diagnostic pitfalls, summary and outlook. *J Neuroinflammation* 2015;12:168.
[PubMed: 26377319]

MULTIPLE SYSTEM ATROPHY (TYPE C)

ESSENTIALS OF DIAGNOSIS

- Chronic, progressive ataxia with associated autonomic instability and/or parkinsonism
- Occurs in patients with no family history of the condition
- Olivopontocerebellar atrophy seen on MRI of the brain

General Considerations

Multiple system atrophy (MSA) is a so-called *Parkinson-plus* syndrome, that is, one of a group of related movement disorders presenting with prominent parkinsonism, autonomic dysfunction, or cerebellar signs (see Chapters 15 and 21). These symptoms and signs may be present in any combination.

Pathogenesis

Neurodegeneration occurs in multiple regions, including the substantia nigra, putamen, cerebellum, olivary nucleus, and pontine nuclei. Glial cytoplasmic inclusions form within the oligodendroglia. These inclusions contain α-synuclein, significant for its role in Parkinson disease pathogenesis.

Clinical Findings

A. Symptoms and Signs

MSA is sporadic, presenting in patients without a positive family history. It is a progressive disease, with adult onset, and typically a faster course than Parkinson disease; in one series of 35 patients, median survival was 7.3 years. The diagnosis is suggested by a combination of cerebellar signs, including an unsteady wide-based gait, dysarthria or scanning speech, along with bradykinesia and rigidity, although patients may present with isolated ataxia. Autonomic dysfunction is a hallmark, pyramidal signs occur in up to half of MSA-C patients, and cognitive changes occur in many.

B. Imaging Studies

CT or MRI scan typically reveals pancerebellar and brainstem atrophy. The cross sign of hyperintensity in the pons on T2-weighted MRI images arises from demyelination of transverse pontine fibers. A thin band of MRI T2-weighted hyperintensity may arise in the dorsolateral margin of the putamen. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) may be useful in some cases to differentiate MSA from Parkinson disease and other related disorders, but they are not widely available.

C. Special Tests

Autonomic dysfunction may be investigated with tilt table and other formal autonomic testing, neurogenic sphincter electromyography, and investigations of neurogenic bladder, as well as patterns of plasma levels of catecholamines and metabolites (see Chapter 21). However, these findings are not specific to MSA.

Differential Diagnosis

Causes of acquired ataxias, including nutritional and associated systemic disease, need to be ruled out. Some patients with apparent sporadic ataxia turn out to have mutations in one of the *SCA* genes (see later discussion).

Treatment

There is currently no disease-specific treatment for MSA. Parkinsonian symptoms improve in some patients treated with levodopa, although the response is rarely as marked as in idiopathic Parkinson disease. Unlike Parkinson disease, deep brain stimulation surgery does not appear to help MSA. Standing blood pressures may be improved by increasing salt in the diet or with use of fludrocortisone, midodrine, or droxidopa, but the risk of supine hypertension necessitates careful monitoring. Elastic stockings are beneficial for some patients. Postprandial hypotension can be reduced by having more frequent, small meals and in refractory cases with octreotide. Urge incontinence can be treated with anticholinergic medications or desmopressin. Incomplete bladder emptying with a residual of 100 mL of urine or more requires self catheterization. Sildenafil citrate can be used for erectile dysfunction, but caution must be advised because it can cause orthostatic hypotension. For constipation, sufficient fluid intake and macrogol water solution may alleviate symptoms. Inspiratory stridor, which is potentially fatal, can be reduced with continuous positive airway pressure treatment. Selective serotonin receptor inhibitors and psychotherapy are recommended for depression. Several agents have been tested for potential disease modification, but without success. However, a study assessing mesenchymal stem cell therapy suggested that this may be a potential option in the future, thus requiring further investigation.

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INHERITED ATAXIAS

There exists a bewildering array of genetically inherited diseases in which ataxia may occur. Recent advances have focused attention on hereditary disorders in which ataxia is the most prominent feature. Despite limitations in treatment, it is important for the clinician to recognize these diseases in order to advise the patient and family appropriately. Ataxia may also occur in several hereditary disorders associated with other complaints, such as developmental delay or epilepsy; these include inborn errors of metabolism, leukodystrophies, and storage disorders.

AUTOSOMAL DOMINANT CEREBELLAR ATAXIAS

1. Spinocerebellar Ataxias

ESSENTIALS OF DIAGNOSIS

- Chronic, progressive cerebellar ataxia
- Family history of cerebellar ataxia (usually)
- Associated features that include oculomotor disturbance, hyperreflexia, macular degeneration (SCA7), dementia (SCA10)
- Genetic testing is available for a subset of these diseases

General Considerations

Spinocerebellar ataxias (SCAs) are a set of genetically and clinically heterogeneous diseases that have in common progressive ataxia. SCAs are now classified genetically according to a specific mutation or mapped locus and also according to clinical features (Table 16–6). In some cases, identification of the gene involved has clarified links to other disorders; for example, mutations in the calcium channel, voltage-dependent, P/Q type, α_{1A} subunit may lead to SCA6, to episodic-ataxia type 2 (see Table 16–8), or to familial hemiplegic migraine, and mutations in the inositol 1,4,5-triphosphate receptor type 1 gene lead to SCA15, SCA16, and SCA29. Dentatorubropallidoluysian atrophy (DRPLA), has not been assigned an SCA number but is considered alongside the SCAs because of some similarities in presentation. In the older literature, a simpler clinical classification used three major categories of autosomal dominant cerebellar ataxia (ADCA), described along with their correspondence to SCAs in Table 16–7. To add to the confusion, many of these diseases have additional names in common use in the literature, for example SCA3 is also known as Machado-Joseph disease.

Table 16–6.

Autosomal-dominant spinocerebellar ataxias.

Name	Distinguishing clinical features	Normal Alleles	Mutation and Alleles	Protein
SCA1	Pyramidal signs, executive dysfunction (rarely overt dementia), hypermetric saccades	CAG 6–44	CAG 39–91	Ataxin-1
SCA2	Slowed saccades, peripheral neuropathy, extrapyramidal signs (rare), myoclonus or action tremor, bulbar signs, dementia, rare pyramidal signs and may be hyporeflexia	CAG 14–31	CAG 33–202	Ataxin-2
SCA3	Gaze-evoked nystagmus, lid retraction, prominent spasticity, bulbar signs, peripheral neuropathy (variable), extrapyramidal signs including parkinsonism, dystonia, ophthalmoparesis, fasciculations of face and tongue, amyotrophy	CAG 12–44	CAG 52–86	Ataxin-3 (MJD1)
SCA4	Cerebellar syndrome, sensory neuropathy (variable)	—	—	—
SCA5	Pure cerebellar syndrome	—	Missense mutation Deletions	Beta-III spectrin
SCA6	Pure cerebellar syndrome, often late onset (>50 y), pyramidal signs (variable)	CAG 4–18	CAG 20–33	Calcium channel, voltage-dependent, P/Q type, α_{1A} subunit

SCA7	Progressive pigmentary retinopathy and macular degeneration with visual loss, hearing loss; childhood onset may be severe, with developmental delay, hypotonia, and sometimes cardiac failure, microcephaly, hemangiomas, hepatomegaly	CAG 4–19	CAG 36–460	Ataxin-7
SCA8	Cerebellar syndrome, spasticity, hyperreflexia, sensory neuropathy in some, slow progression; congenital onset severe with epilepsy, static encephalopathy	CTG/CAG 15–50	CTG/CAG 80–300 (expanded repeats occasionally seen in healthy subjects, psychiatric disease)	Ataxin-8
SCA9	Ophthalmoplegia, some with optic atrophy, parkinsonism, pyramidal signs, weakness	—	—	—
SCA10	Cerebellar syndrome ± seizures, cognitive decline insome	ATTCT 10–32	ATTCT 800–4500	Ataxin-10
SCA11	Pure cerebellar syndrome, hyperreflexia, nystagmus, slowly progressive	—	Stop/frameshift insertion/deletion	Tau tubulin kinase 2
SCA12	Early arm tremor, hyperreflexia in most, ± facial myokymia, peripheral neuropathy, dystonia in a few parkinsonian features, dementia in some	CAG 4–32	CAG 51–78	Protein phosphatase 2, regulatory subunit B, β isoform
SCA13	Ataxia, ± mental retardation, early childhood onset	—	Missense mutation	Voltage-gated potassium channel, Shaw-related subfamily member 3 (KCNC3)
SCA14	Ataxia, myoclonus (with early onset), cognitive impairment, slow progression	—	Missense mutations	Protein kinase C, gamma polypeptide
SCA15	Pure cerebellar syndrome, very slow progression	—	Missense mutations, deletions	inositol triphosphate receptor type 1
SCA16 (same gene as SCA15)	Pure cerebellar ataxia, head & hand tremor	—	Missense mutation	inositol triphosphate receptor type 1
SCA17	Dysphagia, intellectual deterioration to overt dementia, absence seizures, extrapyramidal signs (facial dyskinesia, limb dystonia, chorea, parkinsonism)	CAG/CAA 25–42	CAG/CAA 45–66	TATA box-binding protein
SCA18	Muscle atrophy, vibratory and proprioceptive sensory loss with axonal neuropathy	—	Missense mutation	Inteferon-related developmental regulator 1
SCA19	Mild cognitive impairment, myoclonus, slow irregular postural tremor	—	Missense mutations,	Voltage-gated

			deletions	potassium channel Kv4.3 (KCND3)
SCA20	Palatal tremor, dysphonia, dentate calcification on CT of brain	—	—	—
SCA21	Extrapyramidal features (akinesia, rigidity, tremor), cognitive impairment	—	Missense mutation, truncating mutation	Transmembrane protein 240
SCA22 (same gene as SCA19)	Pure cerebellar syndrome, cognitive impairment, myoclonus, tremor	—	Missense mutations, deletions	Voltage-gated potassium channel Kv4.3 (KCND3)
SCA23	Pyramidal signs, sensory loss	—	Missense mutation	prodynorphin
SCA24	Saccadic intrusions and increased saccadic speed, myoclonus, sensory neuropathy			
SCA25	Profound sensory neuropathy, severe cerebellar atrophy	—	—	—
SCA26	Pure cerebellar syndrome	—	Missense mutation	Eukaryotic translation elongation factor 2
SCA27	Ataxia, tremor, orofacial dyskinesia, cognitive decline, mild axonal sensory neuropathy, pes cavus in a few	—	Missense mutation	Fibroblast growth factor 14 (FGF14)
SCA28	Ophthalmoparesis, ptosis, pyramidal signs	—	Missense mutation	ATPase family gene 3-like 2
SCA29 (same gene as SCA15, SCA16)	Congenital or shortly after, mild developmental delay, slowly progressive	—	Missense mutation	Inositol triphosphate receptor type 1
SCA30	Pure cerebellar syndrome, minor pyramidal signs	—	—	—
SCA31	Pure ataxia, progressive sensorineural hearing impairment	TGGAA repeat 1.5–2.0kb	TGGAA repeat insertion 2.5–3.8kb	Unclear: insertion within intron shared by 2 genes (BEAN, thymidine kinase)
SCA32	Cognitive impairment, azoospermia	—	—	—
SCA33	Not assigned			
SCA34	Infant onset, neurocutaneous syndrome, diminished reflexes	—	Missense mutation	Elongation of very long chain fatty acids protein 4

SCA35	Pseudobulbar palsy, hyperreflexia, torticollis, reduced position sense, tremor	—	Missense Mutation	Transglutaminase6
SCA36	Motor neuron dysfunction, acoustic dysfunction	GGCCTG 3–8	GGCCTG 1700–2300	Nucleolar protein 56
SCA37	Slowly progressive, abnormal eye movements	—	—	—
SCA38	Adult onset, pure ataxia, axonal neuropathy	—	Missense mutation	Elongation of very long chain fatty acids protein 5
SCA39	Not assigned			
SCA40	Spasticity, adult onset	—	Missense Mutation	Coiled-coil domain containing 88C
SCA41	One case of adult progressive cerebellar ataxia; brain MRI mild vermian atrophy	—	Single variant; heterozygous p.Arg762His	TRPC3 (important for channel gaiting)
SCA42	Gait instability (which can remain stable); some with saccadic pursuit, horizontal nystagmus, hyperreflexia, spasticity, depression, and cognitive impairment	—	C.5144g>A mutation, causing an arginin- to-histadine change (p.Arg1715His)	CACNA1G (T-type voltage gated Ca channel)
DRPLA	Onset at age 30 but can occur at any time from infancy to adulthood-ataxia, progressive intellectual deterioration, myoclonus, epilepsy	CAG 6–35	CAG ≥ 48	Atrophin-1
ADCA-DN	Onset in second to fourth decade Hearing loss, ataxia followed by narcolepsy and cognitive decline	—	Global methylation changes	DNMT1

CT = computed tomography; DRPLA = dentatorubropalliodoluysian atrophy; MJD = Machado-Joseph disease; SCA = spinal cerebellar ataxia; ADCA-DN: autosomal dominant cerebellar ataxia with deafness and narcolepsy; DNMT1 = DNA methyl transferase 1.

Table 16–7.

Correspondence of ADCA types I to III with SCA genes.

ADCA	Clinical Features	SCA
ADCA type I (ADCA I)	Cerebellar ataxia *plus* • Spasticity (pyramidal signs) • Supranuclear ophthalmoplegia • Extrapyramidal signs • Peripheral neuropathy (sensory, motor or both) • Cognitive deficit, dementia	SCA1, SCA2, SCA3, SCA4, SCA8, SCA10, SCA12, SCA13, SCA14, SCA15, SCA16, SCA17, SCA18, SCA19, SCA20, SCA21, SCA22, SCA23, SCA25, SCA27, SCA28
ADCA type II (ADCA II)	Cerebellar ataxia *plus* • pigmentary macular degeneration • Other CNS or PNS involvement, as in ADCA I	SCA7
ADCA type III (ADCA III)	Pure cerebellar ataxia *plus* • Mild spasticity (pyramidal signs) • Tremor and nystagmus (SCA5) • Sensorineural hearing loss (SCA31)	SCA5, SCA6, SCA11, SCA26, SCA29, SCA30, SCA31

The following ataxias have not been assigned to ADCA types I to III: SCA 9, 24, 32, 34, 35, 36, 37, 38, 40, 41, 42, DRPLA, DNMT1.

Table 16–8.

Inherited episodic ataxias.

Name	Clinical features	Gene/Inheritance	Treatment
Type 1 (EA-1)	Onset childhood–2nd decade Episodes of ataxia and dysarthria lasting seconds to minutes Provoked by startle and movements Interictal periorbital or hand muscle myokymia but no interictal ataxia Neuromyotonia, seizure, and skeletal deformities in some Variants from this gene include: neuromyotonia and stiffness, chronic neuromyotonia with disappearance of ataxia, severe neuromyotonia and skeletal deformities, episodic ataxia plus paroxysmal dyspnea, fixed ataxia, hypomagnesemia	*KCNA1*-deficiency in voltage-gated potassium channel function Episodic ataxia evaluation panel commercially available. Autosomal dominant	Acetazolamide, 500mg-700mg per day if needed: response is less predictable than EA-2 Phenytoin and carbamazepine if acetazolamide treatment is unsuccessful Counseling to avoid sudden movements

			when possible
Type 2 (EA-2)	Onset childhood–teens Episodes of ataxia and dysarthria lasting 0.5–6 h, nausea, headache, dystonia and seizures in some, hemiplegia in 10% Provoked by emotional stress, physical exertion, heat, alcohol Interictal downbeat or gaze-evoked nystagmus Migraine may be present Interictal ataxia may slowly progress and become persistent, weakness may occur before or during spells MRI may demonstrate atrophy of cerebellar vermis	1. *CACNA1A*-subunit of P/Q-type calcium channel; different mutations in the same gene lead to SCA6 and familial hemiplegic migraine (see Chapter 8) 2. CACNB4 dihydropyridine-sensitive L-type calcium channel Episodic ataxia evaluation panel commercially available Autosomal dominant	Acetazolamide up to 1000mg per day 4-aminopyridine 5 mg three times daily Phenytoin and carbamazepine may exacerbate symptoms
Type 3 (EA-3)	Periodic vestibulocerebellar ataxia with vertigo, diplopia, weakness, tinnitus, interictal myokymia Attacks last minutes to up to six hours	Unknown Chromosome 1q42 Autosomal dominant	Acetazolamide
Type 4 (EA-4)	Onset 3rd–6th decade Episodic ataxia, vertigo, diplopia, slowly progressive ataxia and defective smooth pursuit	Unknown Autosomal dominant	No response to acetazolamide
Type 5 (EA-5)	Onset 3rd–4th decade Episodic ataxia (typically hours), interictal ataxia with mild dysarthria and nystagmus (downbeat and gaze-evoked), also associated with JME, seizures	CACNB4 calcium channel Episodic ataxia evaluation panel commercially available Autosomal dominant	Acetazolamide
Type 6 (EA-6)	Onset in childhood Episodic ataxia with hypotonia lasting 2–4 days Delayed milestones Associated with migraine, alternating hemiplegia, hemianopia, seizures, coma Interictal mild truncal ataxia, increased tendon reflexes, mild static encephalopathy Provoked by fever MRI mild cerebellar atrophy, FLAIR hyperintensity during episodes; EEG seizure activity	EAAT1 glial glutamate transporter Episodic ataxia evaluation panel commercially available Autosomal dominant or sporadic	
Type 7 (EA-7)	Onset < 20 y Paroxysmal ataxia with dysarthria, weakness, vertigo in some lasting hours to days Interictal mild truncal ataxia, increased tendon reflexes, mild static encephalopathy Associated with migraine, alternating hemiplegia, hemianopia, seizures, coma Provoked by exercise, excitement	Unknown Chromosome 19q13 Multiple inheritance patterns	
Type 8 (EA-8)	Vertigo, weakness Attacks last from minutes to up to a day	UBR4: Ubiquitin-protein ligase No commercial testing available Autosomal dominant	

EA+ Choreoathetosis and spasticity (also named DYT9—see Chapter 15)	Onset 2–15 y EEG slowing Episodic ataxia lasting 20 minutes (2/d–2/y) with dystonia, headache, perioral and leg paresthesias Persistent spastic paraplegia Provoked by alcohol, fatigue, physical exercise	Unknown Chromosome 1p	Acetazolamide

CACNA1A = Cav2.1 P/Q voltage-dependent calcium channel; CACNB4 = voltage-dependent L-type calcium channel subunit β4; EAAT1 = excitatory amino acid transporter; DYT9 = dystonia gene 9; EMG = electromyography; JME = juvenile myoclonic epilepsy; KCNA1 = potassium voltage-gated channel subfamily A member 1; MRI = magnetic resonance imaging.

Prevalence of all dominantly inherited progressive ataxias is an estimated 0.9–1.3 cases per 100,000 people. Subtype prevalence depends on geographic location, but the most common ADCAs worldwide are SCA1 (6%), SCA2 (15%), SCA3 (21%), SCA5 (15%), SCA7 (5%), and SCA8 (3%).

Pathogenesis

Many of the known mutations involve expansion of a trinucleotide $(CAG)_n$ repeat within the coding region of the respective gene (see Table 16-6). This is translated into an abnormal polyglutamine tract in the corresponding protein, with formation of nuclear aggregates. The exact pathogenesis is unknown.

Prevention

Genetic testing is available for a subset of SCAs, and it can help obtain a molecular diagnosis to aid in counseling and to define options for participation in research. Some individuals from ataxia-affected families request predictive and, occasionally, prenatal testing. Thorough and careful genetic counseling with a specialist trained in this area is mandated, both for diagnostic and predictive testing. There is no known intervention to delay symptom onset or to slow disease progression.

Clinical Findings

A. Symptoms and Signs

All SCAs produce a progressive cerebellar syndrome with gait and appendicular ataxia, dysarthria, and oculomotor disturbances. Patients may also have dysphagia; spasticity; brisk tendon reflexes with extensor plantar responses; noncerebellar oculomotor features; and signs of brainstem disease, such as facial atrophy and fasciculations. There is a tremendous heterogeneity within each type, as well as clinical overlap between types (see Table 16–6). Even within those SCAs caused by expanded trinucleotide repeats, age of onset varies widely; typically onset is in the 30s for SCA1, SCA2 and SCA3, but later for SCA6, and it may be inversely correlated with repeat expansion length. Additionally, the phenomenon of anticipation may be observed within a family, with an earlier age of onset and more severe phenotype in successive generations because of a tendency of expanded repeats to increase progressively from generation to generation. Because of clinical overlap, individual SCAs cannot be easily differentiated by clinical or imaging studies alone. Genetic testing is the only means to make a definitive diagnosis in a given patient.

B. Imaging Studies

There are no features specific for SCAs, but cerebellar or olivopontocerebellar atrophy is often revealed by MRI. Cerebral cortical atrophy may be observed in some. Cerebral white matter abnormalities may be seen in DRPLA.

C. Special Tests

Genetic testing is commercially available for several SCAs and for DRPLA. A genetic cause may be assumed in patients with a clear family history. In sporadic cases, it is less clear when to test: mutations, including SCA1, SCA2, SCA3, and SCA6, have been detected. In patients with a negative family history (ie, three or more generations without ataxia), yield of testing for SCAs is low. However, testing may be considered if a sporadic case has features very similar to one of the inherited ataxias. Erroneous assignment of paternity should also be kept in mind when recording family history.

Despite careful evaluation and consideration of testing, some patients with clear evidence of autosomal dominant inheritance do not obtain a clear molecular diagnosis because available tests do not cover all the known (and unknown) SCAs.

Treatment

There is no treatment to prevent neuronal cell death in ADCA, although patients may choose to participate in clinical trials of experimental treatments (an updated list is kept at the website www.clinicaltrials.gov). For symptomatic treatment, guidelines follow those for any ataxic patient. Ataxia-specific drugs are lacking. However, a recent randomized, double-blind, placebo-controlled study of 55 patients with hereditary ataxias has suggested that riluzole could provide benefit. This requires further study before it is adopted in the clinic. Parkinsonism may respond to levodopa or other dopaminergic medications. Seizures are treated with antiepileptic medications, and if myoclonus is debilitating, benzodiazepines, valproic acid, and levetiracetam are options. Spasticity is treated with baclofen, up to 20 mg four times daily; alternatives include benzodiazepines, tizanidine, and botulinum toxins. Dystonia, if present, is treated as described in Chapter 15.

Prognosis

All SCAs are characterized by a progressive course, but there is tremendous variation in rate of progress and prognosis. Time from symptom onset to death typically ranges from one to three decades. However, progression is particularly slow in SCA5, SCA13, and SCA21, and patients with SCA8 and SCA11 typically have a normal lifespan.

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2. Episodic Ataxias

ESSENTIALS OF DIAGNOSIS

- Episodes of ataxia and dysarthria lasting from seconds to minutes (type 1 disease) or hours to days (type 2)
- Provocation of episodes by startle and movement (type 1) or emotional stress and change of body position (type 2)
- Often associated with migraine (type 2)
- Interictal periorbital or hand muscle myokymia (type 1) or gaze-evoked or downbeat nystagmus (type 22)
- Autosomal dominant inheritance

General Considerations

Eight different forms of episodic ataxia (EA) have been described to date. By far the most common are EA1 and EA2. Features of these rare disorders are summarized in Table 16–8.

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AUTOSOMAL RECESSIVE CEREBELLAR ATAXIAS

Friedreich ataxia and ataxia telangiectasia are the most common cerebellar ataxias inherited in an autosomal recessive fashion. Table 16–9 lists other autosomal recessive ataxias that, although extremely rare, should be recognized because of existing treatment options. Treatable ataxias include abetalipoproteinemia, ataxia with isolated vitamin E deficiency, hereditary motor and sensory neuropathy type IV, and cerebrotendinous xanthomatosis. Wilson disease, a treatable disorder resulting from copper accumulation and subsequent hepatic dysfunction, has variable presentations, but cerebellar symptoms may be present and tremor appears in up to 50% of patients. Wilson disease is discussed in Chapter 15.

Table 16–9.

Rare autosomal recessive cerebellar ataxias (ARCA).

Name	Clinical features	Gene	Protein	Treatment
Abetalipoproteinemia, Bassen-Kornzweig syndrome	Neuronal-cerebellar ataxia, pigmentary degeneration of the retina, progressive ataxic neuropathy (large fiber, demyelinating, sensory) Non-neuronal-defective intestinal lipid resorption, very low serum cholesterol levels, absent serum betalipoprotein, celiac syndrome, acanthocytosis	*MTP*	Microsomal triglyceride transfer protein	Vitamin E 50-100 IU/kg/day
Hereditary motor and sensory neuropathy	Neuronal-retinitis pigmentosa, chronic demyelinating polyneuropathy, cerebellar ataxia, nerve deafness, anosmia	PHYH, PAHX,	Phytanoyl-CoA hydroxylase	Dietary restriction of phytanic acid,

IV (HMSN IV), Refsum disease	Non-neuronal-ichthyosis, cardiomyopathy with sudden cardiac death, skeletal deformities including short 4th metatarsal, epiphyseal dysplasia, syndactyly	PEX1, PEX7	PTS2 receptor	acute worsening by plasma exchange
Cerebrotend-inous xanthomat-osis	Neuronal-cerebellar ataxia, systemic spinal cord involvement, dementia, and later brainstem signs leading to death Non-neuronal-chronic diarrhea, premature atherosclerosis, widespread deposits of cholesterol and cholestanol, particularly in Achilles tendons, brain, and lungs. Elevated cholestanol in serum, cataracts MRI-diffuse/cerebellar atrophy, bilateral focal cerebellar lesions	*CYP27A1, CTX*	Cytochrome P450, subfamily XXVIIA, polypeptide 1 (sterol 27-hydroxylase)	Chenodeoxycholate 750mg/day
Ataxia with oculomotor apraxia (AOA1)	Neuronal-resembles ataxia-telangiectasia, progressive ataxia in early stages, progressive axonal motor neuropathy, variable oculocephalic dissociation, can have chorea dn/or dystonia Non-neuronal-low albumin, high cholesterol, no immunodeficiency or increased risk for malignancies MRI-cerebellar atrophy	*APTX, AOA1*	Aprataxin Gene sequencing commercially available	
Ataxia with oculomotor apraxia (AOA2)	Neuronal-chorea, dystonia or both may be present; variable oculocephalic dissociation present Non-neuronal-elevated alpha fetoprotein MRI: cerebellar atrophy	*SETX, AOA2*	Senataxin Gene sequencing commercially available	
Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)	Neuronal-ataxia, dysarthria, spasticity, extensor plantar reflexes, distal muscle wasting and sensory-motor neuropathy predominantly in legs, horizontal gaze nystagmus; in Quebec patients only, retinal streaks of hypermyelinated fibers seen in funduscopy. Non-neuronal-none described MRI-cerebellar atrophy sparing pons	*Sacsin*	Sacsin gene test available	
Autosomal recessive cerebellar ataxia type 1	Pure ataxia MRI: cerebellar atrophy	SYNE1	Spectrin repeats-nuclear envelope 1 Complete recessive ataxia panel contains SYNE1 testing	
Niemann-Pick type C	Cognitive dysfunction, dystonia, vertical supranuclear gaze palsy Splenomegaly Positive filipin staining on skin biopsy MRI: variable cerebral and cerebellar atrophy	NPC1 NPC2	Niemann-Pick C1 protein Epididymal secretory protein E1	Miglustat 600mg daily in adults
Congenital disorder of glycosylation Type1A	Epilepsy, thoracic deformity, mental retardation, retinitis pigmentosa Laboratory findings: serum transferrin isoelectric focusing MRI: cerebellar atrophy	PMM2	Phosphormannomutase	
Late onset GM2	Anterior horn involvement, epilepsy, cognitive decline,	Hex A	Hexaminidase A	

gangliosidosis	dystonia, spasticity, weakness, psychosis Hexaminidase A deficiency: late onset Tay Sach's disease Hex A+B deficiency: Sandhoff's disease MRI-cerebellar atrophy	Hex B	Hexaminidase B	

1. Friedreich Ataxia

ESSENTIALS OF DIAGNOSIS

- Chronic, slowly progressive cerebellar ataxia
- Absent lower limb tendon reflexes (variants exist)
- Onset usually between ages 2 and 25 years
- Cardiomyopathy (common)
- Diabetes mellitus (up to 25% of patients)

General Considerations

Friedreich ataxia (FRDA) is the most common of all hereditary ataxias in Caucasians, with a prevalence ranging from 2-4 cases per 100,000 person-years, but it is rare in populations of Asian or African descent. It is caused by a deficiency of the protein frataxin, encoded by the *FRDA1* gene. Approximately 98% of patients have a homozygous allele for an unstable expansion of GAA trinucleotide repeats. Approximately 2% of all FRDA patients have missense, nonsense, or splice mutations, making genetic testing more complex. A second genetic locus, *FRDA2,* has also been described.

Clinical Findings

A. Symptoms and Signs

FRDA is characterized by a slowly progressive gait and limb ataxia, absent lower limb reflexes, and reduction or loss of proprioception and vibration sense. Onset is typically between the ages of 2 and 25 years. The legs may be spastic, and extensor plantar responses may be present. Rarely, other movement disorders, including chorea, or spastic paraparesis may occur. Kyphoscoliosis is an early sign; pes cavus deformity occurs later. Hypertrophic cardiomyopathy is a prominent feature of classic FRDA and leads eventually to death. Diabetes mellitus occurs in later stages in up to 25% of patients and contributes significantly to morbidity and mortality.

Genetic testing has revealed a spectrum of milder cases with later onset and a less debilitating course, as well as other movement disorders. Late-onset FRDA manifests in patients between 26 and 39 years of age, and very late-onset FRDA, after 40. These variants account for approximately 10–15% of known FRDA cases. Another variant is FRDA with retained reflexes, which also has a more benign course.

B. Imaging Studies and Special Tests

Commercial testing is available for trinucleotide repeat expansion in the *FRDA1* gene. MRI demonstrates atrophy of the cerebellum and often the cervical spinal cord. Electrocardiographic studies often show evidence of repolarization abnormalities, which may precede neurologic symptoms. Concentric hypertrophic cardiomyopathy, or other abnormalities, is revealed by echocardiogram in some patients. Electrophysiologic studies can demonstrate absent or reduced-amplitude sensory nerve action potentials.

Treatment

Treatment of FRDA follows guidelines for ataxia in general; no curative treatment is as yet available. Monitoring for cardiomyopathy and diabetes is

undertaken at least yearly. Idebenone, 5 mg/kg/day, reduces cardiac hypertrophy in most patients studied, but does not halt progression of ataxia. Although higher doses have been suggested to alleviate neurologic symptoms, a recent review found only weak evidence to support its use in patients with FRDA. Deferiprone, an iron-chelating agent, was suggested in subgroup analysis of results from a randomized, placebo-controlled clinical trial to slow progression in those with milder disease, but further evidence is required before its use can be recommended.

Prognosis

Many patients are wheelchair-bound 10–20 years after symptom onset. The disease often leads to death in middle age, related to cardiomyopathy, diabetic complications or pneumonia, although there are exceptions.

Bürk K. Friedreich ataxia: Current status and future prospects. *Cerebellum Ataxias* 2017;4:4.
[PubMed: 28405347]

Kearney M, Orrell RW, Fahey M, Brassington R, Pandolfo M. Pharmacological treatments for Friedreich ataxia. *Cochrane Database Syst Rev* 2016;(8):CD007791.
[PubMed: 27572719]

Mariotti C, et al. Idebenone treatment in Friedreich patients: One-year-long randomized placebo-controlled trial. *Neurology* 2003;60:1676.
[PubMed: 12771264]

Pandolfo M, et al. Deferiprone in Friedreich ataxia: A 6-month randomized controlled trial. *Ann Neurol* 2014;76:509–521.
[PubMed: 25112865]

2. Ataxia-Telangiectasia

ESSENTIALS OF DIAGNOSIS

- Slowly progressive ataxia with onset usually in infancy
- Telangiectasias affecting conjunctivae and other structures
- Immunodeficiency (common)
- Malignancies (frequent, particularly in childhood)

General Considerations

Ataxia-telangiectasia is a rare disease affecting the nervous, vascular, and immune systems, but it is the most common inherited progressive ataxia of childhood in most countries, with an incidence of 0.3 cases per 100,000 live births in the United States. It is caused by mutations of the *ATM* gene, one of the phosphatidylinositol-3 kinase family, involved in DNA repair and cell-cycle control. This deficiency is thought to be responsible for predisposition for malignancies and immune deficiency.

Clinical Findings

A. Symptoms and Signs

Disease onset is typically in infancy with truncal and later limb ataxia. Telangiectasias typically are found in the conjunctivae and earlobes. Immunodeficiency in 60–80% of patients often manifests as recurrent pulmonary and sinus infections. Nearly 40% of affected individuals develop malignancies during their lifetime, typically either lymphoma or leukemia, most before 20 years of age. Older patients tend to develop solid tumors, including ovarian cancer, breast cancer, gastric cancer, malignant melanoma, leiomyoma, or sarcoma.

B. Laboratory Findings and Imaging Studies

Elevated α-fetoprotein level is found in more than 90% of patients. Serum levels of IgA, IgE and IgG are decreased. MRI of the brain initially demonstrates a normal cerebellum, but shows considerable cerebellar atrophy by the age of 10 years.

C. Special Tests

Western immunoblot analysis for the intranuclear serine-protein kinase ATM in lymphoid cell lysates demonstrates absent or very low levels of ATM protein. Given the diversity of mutations of the *ATM* gene that cause ataxia-telangiectasia, genetic testing is not used routinely.

Treatment & Prognosis

Guidelines for managing neurologic symptoms follow those for other ataxias. Patients with ataxia-telangiectasia need to be closely monitored for malignancies. In those with tumors, dosages of radiation therapy need to be adjusted because of increased sensitivity to radiation.

The overall prognosis is grave. Most patients are wheelchair-bound by the age of 10, and most die before the age of 30. However, progression is slower in patients with disease of later onset (>30 years).

3. Ataxia With Isolated Vitamin E Deficiency

ESSENTIALS OF DIAGNOSIS

- Slowly progressive ataxia
- Depressed lower limb reflexes
- Onset typically before age 20 years
- Low serum α-tocopherol
- No abnormality of intestinal lipid absorption or other fat-soluble vitamins

General Considerations

Ataxia with isolated vitamin E deficiency (AVED) is caused by mutations in the gene for α-tocopherol transfer protein, which is responsible in the liver for incorporating tocopherols into very-low-density lipoproteins for subsequent release into the circulation. In affected patients, therefore, vitamin E is rapidly eliminated, resulting in deficiency despite adequate enteric resorption. How this leads to neurodegeneration is unclear, but free radical damage and mitochondrial dysfunction have been implicated. Recent animal models suggest that vitamin E deficiency leads to cellular atrophy and reduced dendritic branching of Purkinje cells.

Clinical Findings

A. Symptoms and Signs

The diagnosis of AVED should be considered if a patient presents with clinical features suggestive of FRDA, but molecular testing for the *FRDA* gene mutation is negative. Cardiomyopathy, similar to the one in FRDA, is present in only 20% of affected patients.

B. Laboratory Findings

Serum vitamin E (α-tocopherol) is severely reduced or absent in affected patients. Levels of other lipid-soluble vitamins and β-lipoprotein are normal.

Treatment

Oral supplementation of vitamin E at a dose of 800–2000 IU daily or twice daily is the treatment of choice.

Cavalier L, et al. Ataxia with isolated vitamin E deficiency: Heterogeneity of mutations and phenotypic variability in a large number of families. *Am J Hum Genet* 1998;62:301.
[PubMed: 9463307]

Ulatowski L, et al. Vitamin E is essential for Purkinje neuron integrity. *Neuroscience* 2014;260:120–129.
[PubMed: 24342566]

4. Other Rare Autosomal Recessive Ataxias

Table 16–9 summarizes neuronal and nonneuronal manifestations, clues for diagnosis, and underlying genetic defects of some of a subset of these heterogeneous disorders. Abetalipoproteinemia, hereditary motor and sensory neuropathy type IV, and cerebrotendinous xanthomatosis are amenable to treatment. Other rare ataxias with childhood onset include childhood ataxia with central nervous system hypomyelination (also called *vanishing white matter disease*) and storage and metabolic disorders. Early-onset ataxias are also categorized by associated features including retinal degeneration (Hallgren syndrome), hypogonadism (Holmes syndrome), cataracts and mental retardation (Marinesco-Sjögren syndrome) and myoclonus (Ramsay Hunt syndrome).

Anheim M, et al. The autosomal recessive cerebellar ataxias. *N Engl J Med* 2012;366:636–646.
[PubMed: 22335741]

Bouchard JP, et al. Autosomal recessive spastic ataxia of Charlevoix-Saguenay. *Neuromuscul Disord* 1998;8:474–479.
[PubMed: 9829277]

Le Ber I, et al. Cerebellar ataxia with oculomotor apraxia type 1: Clinical and genetic studies. *Brain* 2003;126:2761–2772.
[PubMed: 14506070]

Le Ber I, et al. Frequency and phenotypic spectrum of ataxia with oculomotor apraxia 2: A clinical and genetic study in 18 patients. *Brain* 2004;127:759–767.
[PubMed: 14736755]

Patterson M. Niemann-Pick disease type C. 2000 [Updated 2013]. In: Pagon RA, et al (eds) *GeneReviews* [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2018.

CEREBELLAR ATAXIA IN MITOCHONDRIAL DISORDERS

ESSENTIALS OF DIAGNOSIS

- Chronic, progressive multisystem disorders
- Common neurologic features—ptosis, external ophthalmoplegia, myopathy, exercise intolerance, sensorineural deafness, optic atrophy, pigmentary retinopathy, dementia or developmental delay, seizures, and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Common nonneuronal features—cardiomyopathy and diabetes mellitus
- Mostly maternal inheritance

General Considerations

Several of the clinically heterogeneous mitochondrial disorders may involve ataxia as part of their clinical course (Table 16–10). Family histories may be complex, with clinical heterogeneity due to organ mosaicism (heteroplasmy) and variable penetrance. These disorders are described fully in Chapter 24 and in the appropriate clinical context should be considered in the ataxic individual. There is, as yet, no treatment for these disorders, with the notable exception of hereditary coenzyme Q10 deficiency; for that reason this disorder is described in more detail here.

Table 16–10.

Mitochondrial disorders producing ataxia.

Name	Clinical features	Diagnostic laboratory clues
Autosomal-recessive mitochondrial ataxic syndrome	Onset often with migraine and epilepsy, with later sensory and cerebellar ataxia	MRI—abnormalities in cerebellum, olivary nucleus, occipital cortex, thalami Muscle biopsy—COX deficiency, depletion of mtDNA. Associated POLG mutations
Chronic progressive external ophthalmoplegia (CPEO)	Ataxia, extraocular muscle weakness, peripheral neuropathy, ataxia, tremor, depression, cataracts, pigmentary retinopathy, deafness, rhabdomyolysis, hypogonadism Can occur with sensory ataxic neuropathy dysarthria and ophthalmoplegia (SANDO) or mitochondrial recessive ataxia syndrome (MIRAS)	Muscle biopsy—variable POLG1 mutation
Familial coenzyme Q10 deficiency	Variable age of onset Ataxia, generalized muscle weakness, pyramidal signs, neuropathy, developmental delay, seizures	Muscle biopsy-reduced levels of CoQ10 MRI-cerebellar atrophy
Infantile onset spinocerebellar ataxia (IOSCA)	Normal development until first year of life with subsequent hypotonia, ataxia, ophthalmoplegia, optic atrophy, hearing loss, sensory axonal neuropathy, female hypogonadism, and epilepsy	Mutation in C10orf2 gene (encoding the Twinkle protein, a DNA helicase necessary for mitochondrial DNA replication)
Kearns-Sayre syndrome (KSS)	Onset before 20 y Ptosis and external ophthalmoplegia, retinopathy, ataxia, absent deep tendon reflexes, cardiomyopathy, short stature, hypogonadism, diabetes mellitus, hypoparathyroidism	Lactic acidosis in serum and CSF, CSF protein > 100 mg/dl muscle biopsy-RRF MRI-sometimes shows leukoencephalopathy, often associated

		with cerebral or cerebellar atrophy or basal ganglia lesions
Maternally inherited Leigh syndrome (MILS)	Onset 3-12 months, often following viral infection Developmental delay, hypotonia, spasticity, chorea, ataxia, dystonia, external ophthalmoplegia, peripheral neuropathy, hypertrophic cardiomyopathy	Lactic acidosis in CSF > serum, elevated plasma alanine, hypocitrullinemia MRI-bilateral symmetric hyperintense signal abnormality in the brainstem and/or basal ganglia on T2-weighted sequences
Maternally inherited diabetes, deafness, with cerebellar ataxia (MIDD)	Ataxia, deafness, diabetes	tRNA(Leu) 3243
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	Onset usually between 4 and 15 y Episodic vomiting, seizures, and recurrent cerebral insults resembling strokes; myoclonic epilepsy; weakness; ataxia; deafness; retinitis pigmentosa; migraine-like headaches, dementia	Lactic acidosis in serum and CSF, elevated CSF protein usually < 100 mg/dL muscle biopsy-RRF MRI-during stroke-like episodes T2-hyperintense lesions not conforming to distribution of major cerebral arteries
Myoclonic epilepsy with red-ragged fibers (MERRF)	Onset in childhood Myoclonic epilepsy, mental deterioration, weakness, truncal ataxia, dementia, spasticity, optic atrophy, peripheral neuropathy, deafness, cardiomyopathy with Wolf-Parkinson White syndrome	Lactic acidosis in serum and CSF muscle biopsy-RRF MRI-brain atrophy, basal ganglia calcifications
Neuropathy, ataxia, and retinitis pigmentosa (NARP)	Typical onset in young adults Developmental delay, retinitis pigmentosa, dementia, seizures, cerebellar ataxia, sensorimotor neuropathy	Lactic acidosis in CSF Hypocitrullinemia MRI: cerebral and cerebellar atrophy
POLG (DNA polymerase γ catalytic subunit) mutations	Pleomorphic disease: ptosis, ophthalmoplegia, limb muscle weakness, sensory neuropathy, cerebellar syndrome, palatal tremor, dystonia, myoclonus, chorea, epilepsy, cognitive impairment, psychiatric issues	Muscle biopsy-large-scale deletions of mitochondrial DNA MRI-mild to no cerebellar atrophy Electrophysiology-sensory axonal neuropathy and impaired central motor conduction

DiMauro S, Schon EA. Mitochondrial disorders in the nervous system. *Annu Rev Neurol* 2008;31:91–123.
[PubMed: 18333761]

Lehman D, et al. Peripheral neuropathy in patients with CPEO associated with single and multiple mtDNA deletions. *Neurol Genet* 2016;2:e113.
[PubMed: 27822509]

Pierce SB, et al. Infantile onset spinocerebellar ataxia caused by compound heterozygosity for Twinkle mutations and modeling of Twinkle mutations causing recessive disease. *Cold Spring Harb Mol Case Stud* 2016;2(4):a001107.
[PubMed: 27551684]

Synofzik, M, et al. Characterizing POLG ataxia: Clinics, electrophysiology, and imaging. *Cerebellum* 2012;11:1002–1011.
[PubMed: 22528963]

Familial Ataxia With Coenzyme Q10 Deficiency

ESSENTIALS OF DIAGNOSIS

- Ataxia and other features, including seizures, peripheral neuropathy, pyramidal signs, and developmental delay
- Low coenzyme Q10 (CoQ10) levels in muscle

General Considerations

Despite its rarity, primary CoQ10 deficiency is important to recognize because it is a potentially treatable cause of progressive ataxia. CoQ10 is a component of the mitochondrial electron transport chain and is a potent antioxidant and membrane stabilizer. Therefore, it is possible that increased oxidative damage plays a role in progressive neurologic deterioration. Mode of inheritance and genetic basis are not yet well characterized.

Clinical Findings

A. Symptoms & Signs

Ataxia can be prominent. Associated signs and symptoms include seizures, weakness, pyramidal signs, peripheral neuropathy, and developmental delay. The disorder can also occur in a myopathic form. Symptom onset is predominantly during infancy or childhood, but adult onset has been reported.

B. Laboratory Findings and Imaging Studies

Pyruvate and lactate levels are normal, and CoQ10 levels in serum may be normal or low. MRI of the brain characteristically reveals cerebellar atrophy, although individual cases may have other features.

C. Special Tests

Diagnosis depends on low CoQ10 levels in muscle. Ragged-red fibers are present in the rare, myopathic form but typically not in the ataxic form.

Treatment & Prognosis

Some patients receiving CoQ10 supplementation (up to 3000 mg/day) show improvement in ataxia, strength, and seizures. Without treatment, symptoms progress. Weakness and wasting may lead to confinement to a wheelchair, and seizures can be difficult to control. Few cases have been characterized, and the true range in prognosis remains to be defined.

Musumeci O, et al. Familial cerebellar ataxia with muscle coenzyme Q10 deficiency. *Neurology* 2001;56:849–855.
[PubMed: 11294920] (First description of six patients with ataxia and other symptoms, with response to CoQ10 supplementation.)

Quinzii CM, et al. CoQ10 deficiency diseases in adults. *Mitochondrion* 2007;7(suppl):S122–S126.
[PubMed: 17485248]

X-LINKED ATAXIAS: FRAGILE X–ASSOCIATED TREMOR & ATAXIA SYNDROME

ESSENTIALS OF DIAGNOSIS

- Ataxia, tremor
- Cognitive decline (some patients)
- Occurs almost exclusively males
- MRI of the brain may show atrophy and abnormal T2-weighted signal in the middle cerebellar peduncle

General Considerations

Expansion of the triplet repeat CGG in the X-linked *FMR1* gene leads to mental retardation and other features of the fragile X syndrome. However, premutation expansions (55–200 repeats) have recently been identified as the cause of cerebellar tremor and ataxia in older male carriers without fragile X syndrome. Forty percent of male carriers and 16% of the female carriers of the premutation older than the age of 50 years have the core neurologic features of intention tremor and gait ataxia.

Clinical Findings

A. Symptoms and Signs

Symptoms usually begin with progressive action tremor. Gait ataxia follows, and associated features include parkinsonism, peripheral neuropathy, autonomic dysfunction, and impaired memory and executive function. Depression and anxiety occur in some. Some patients present with isolated cerebellar ataxia. Recently, olfactory dysfunction was also found to be common in fragile X–associated tremor/ataxia syndrome (FXTAS).

B. Imaging Findings

MRI of the brain demonstrates generalized atrophy, including the cerebellum. Approximately 60% of male patients studied have increased signal intensity on T2-weighted images within the middle cerebellar peduncle (MCP). Other findings on MRI may include increased white matter hyperintensities in the pons, splenium of the corpus callosum and periventricular region, and thinning of the corpus callosum. Definite FXTAS is defined as the presence of the MCP sign with ataxia or intention tremor or a positive genetic test (see below). Probable diagnosis is made with the presence of the MCP sign and one minor symptom such as parkinsonism or the presence of both major criteria (ataxia and intention tremor). Possible diagnosis is made when either ataxia or intention tremor are present along with one minor radiologic criteria (cerebral white matter hyperintensities or moderate to severe generalized atrophy).

C. Special Tests

Diagnosis is made by commercially available genetic testing for trinucleotide repeat expansion within the *FMR1* gene.

Treatment

No disease-specific treatment is available, but symptom-targeted therapies are often used. Action tremor sometimes responds to β-adrenergic blocking agents or primidone. Physical therapy for gait can be prescribed. Memantine and acetylcholinesterase inhibitors may be given for cognitive issues. Case reports have suggested a role for venlafaxine in improving attention.

Hagerman R, Hagerman P. Advances in clinical and molecular understanding of the FMR1 premutation and fragile X-associated tremor/ataxia syndrome. *Lancet Neurol* 2013;12:786–798.
[PubMed: 23867198]