Ataxia

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ABSTRACT

Purpose of Review: This article introduces the background and common etiologies of ataxia and provides a general approach to assessing and managing the patient with ataxia.

Recent Findings: Ataxia is a manifestation of a variety of disease processes, and an underlying etiology needs to be investigated. Pure ataxia is rare in acquired ataxia disorders, and associated symptoms and signs almost always exist to suggest an underlying cause. While the spectrum of hereditary degenerative ataxias is expanding, special attention should be addressed to those treatable and reversible etiologies, especially potentially life-threatening causes. This article summarizes the diseases that can present with ataxia, with special attention given to diagnostically useful features. While emerging genetic tests are becoming increasingly available for hereditary ataxia, they cannot replace conventional diagnostic procedures in most patients with ataxia. Special consideration should be focused on clinical features when selecting a cost-effective diagnostic test.

Summary: Clinicians who evaluate patients with ataxia should be familiar with the disease spectrum that can present with ataxia. Following a detailed history and neurologic examination, proper diagnostic tests can be designed to confirm the clinical working diagnosis.

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INTRODUCTION

Ataxia, defined as impaired coordination of voluntary muscle movement, is a physical finding, not a disease, and the underlying etiology needs to be investigated. Ataxia can be the patient's chief complaint or a component among other presenting symptoms. Ataxia is usually caused by cerebellar dysfunction or impaired vestibular or proprioceptive afferent input to the cerebellum. Ataxia can have an insidious onset with a chronic and slowly progressive clinical course (eg, spinocerebellar ataxias [SCAs] of genetic origin) or have an acute onset, especially those ataxias resulting from cerebellar infarction, hemorrhage, or infection, which can have a rapid progression with catastrophic effects. Ataxia can also have a subacute onset, as from infectious or immunologic disorders, which may have a limited window of therapeutic opportunities. A prompt management strategy for treatable causes of ataxia can save the patient's life and result in a good long-term outcome. Ataxia can also be benign in largely symptomatic disorders (eg, vestibular neuritis). With the advancement of neurogenetics, more inherited causes of cerebellar ataxia can be diagnosed,[1,2] but many sporadic ataxias, including those with a chronic and progressive course, still remain undiagnosed.[3] It cannot be overemphasized that it is easy to give a label of a neurodegenerative cause, but finding a reversible and treatable etiology should be sought. The evaluation of ataxia has been reviewed with many different approaches.[4–7] This article introduces symptomatology, neuroanatomy, classification, and common etiologies of ataxia and provides a practical approach to the evaluation of ataxia.

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SYMPTOMS AND SIGNS OF ATAXIA

Symptoms and signs are often related to the location of the lesions in the cerebellum. Lateralized cerebellar lesions cause ipsilateral symptoms and signs, whereas diffuse cerebellar lesions give rise to more generalized symmetric symptoms. Lesions in the cerebellar hemisphere produce limb (appendicular) ataxia. Lesions of the vermis cause truncal and gait ataxia with limbs relatively spared. Vestibulocerebellar lesions cause disequilibrium, vertigo, and gait ataxia. Acute pathology in the cerebellum may initially produce severe abnormalities; this may recover remarkably with time and can become asymptomatic even when imaging shows persistent dramatic structural changes in the cerebellum. Chronic progressive ataxia is not only due to neurodegenerative or inherited cerebellar diseases but also neoplasms and chronic infections.

Terms Describing Ataxia

The following clinical terms are often used in describing ataxia.

Stance. A healthy person can stand naturally with feet spread less than 12 cm apart and is able to stand stable with feet together or in tandem for more than 30 seconds. An impaired stance in the absence of motor weakness or gross involuntary movements is suggestive of cerebellar ataxia or sensory ataxia.

Gait ataxia. Gait ataxia results from incoordination of the lower extremities due to cerebellar pathology or loss of proprioceptive input. Patients often feel insecure and have to hold onto the wall or furniture and walk with feet apart. An increased gait disturbance when visual cues are removed (walking with eyes closed or in the dark) suggests a sensory or vestibular component to the ataxia. With cerebellar causes, the gait ataxia remains the same regardless of visual cues.

Sensory ataxia. Sensory ataxia is mainly reflected by gait disturbance, as previously described. In addition, subjects with sensory ataxia will have a positive Romberg sign. Subjects may walk with a high-stepping gait (due to associated motor weakness) or feet-slapping gait (to assist with sound-induced sensory feedback). Pseudoathetosis (random finger movements seen on outstretched hands with eyes closed) may also occur in sensory neuronopathy affecting the upper limbs.

Truncal ataxia. Truncal ataxia may result from midline cerebellar lesions. Patients may present with truncal instability in the form of oscillation of the body while sitting (worse with arms stretched out in front) or standing (titubation).

Limb ataxia. Limb ataxia is often used to describe ataxia of the upper limbs resulting from incoordination and tremor and can be better described by functional impairment, such as clumsiness with writing, buttoning clothes, or picking up small objects. The patient has to slow down the movement to be accurate in reaching things. Limb ataxia can be lateralized with ipsilateral cerebellar lesions.

Dysdiadochokinesia/dysrhythmokinesis. Dysdiadochokinesia/dysrhythmokinesis is tested by rapidly alternating hand movements or tapping the index finger on the thumb crease. Impairment can be seen with irregularity of the rhythm and amplitude.

Intention tremor. Intention tremor results from instability of the proximal portion of the limb and is manifested by increasing amplitude of oscillation at the end of a voluntary movement. It is often tested by finger-to-nose and heel-to-shin maneuvers. This is different from essential tremor, which primarily occurs in the distal portion of the limb.

Dysmetria. Dysmetria is when the patient misses the targeted object either due to overshoot (hypermetria)

or undershoot (hypometria). Dysmetria is often tested by a finger-chasing test and can be quantified by the distance (cm) that is missed. Dysmetria also happens when the eyes switch objects (ocular dysmetria); either the eyes need a second move to catch the object (hypometric saccades) or have to correct the overshoot to focus on the object (hypermetric saccades). The shin-tap test (accurate tapping of midshin or knee with a heel of the opposite leg) also tests for dysmetria.

Dysarthria/scanning speech. Dysarthria is often described by the patient or relatives as slurred speech. The patient's speech is irregular and slow with unnecessary hesitation. Words are often broken into separate syllables, and some syllables with a plosive consonant are unusually stressed (scanning speech).

Nystagmus. Nystagmus often occurs in cerebellar disease. Lateral gaze-evoked nystagmus is seen by slow drift toward midline followed by a fast phase of saccades to the eccentric position. Upbeat and downbeat nystagmus are defined by the rapid phase in the up or down direction. Upbeat nystagmus is seen in lesions of the anterior vermis. Downbeat nystagmus is typically seen in a lesion in the foramen magnum such as an Arnold-Chiari malformation.

Saccades. Saccade speed is typically normal in cerebellar disease but often an overshoot or undershoot (ocular dysmetria) is present, and is often followed by a corrective saccade in the appropriate direction. However, in SCA type 2 (SCA2) and advanced stages of other SCAs, saccades are slowed (**Supplemental Digital Content 9-1**, *links.lww.com/CONT/A196*).

Square-wave jerks/ocular flutter/opsoclonus. Square-wave jerks, ocular flutter, and opsoclonus are terms used to describe other ocular disturbances in cerebellar disease. Square-wave jerks appear as two saccades in opposite directions separated by a short period of no movement. A healthy person may have a 0.1- to 0.3-degree square-wave movement but have less than 10 per minute. Large-amplitude square-wave jerks are more specific of cerebellar ataxia. Ocular flutter differs from square-wave jerks in that the repetitive saccades are not separated by short periods of no movement. Opsoclonus is continuous conjugate saccades in all directions in a chaotic fashion. Both ocular flutter and opsoclonus are generally indicative of cerebellar disease from paraneoplastic (neuroblastoma) or postinfectious syndromes (as can be seen in opsoclonus-myoclonus ataxia).

Neurologists should be familiar with the specific ataxia terms and use them appropriately in documentation and communication with colleagues. It is important to understand the nomenclature because it often implies a certain ataxic disorder.

NEUROANATOMY OF ATAXIA

The cerebellum and its afferent and efferent connections, the vestibular system, and the proprioceptive sensory pathway (**Figure 9-1**) are all involved in ataxia. The cerebellum is usually separated into the midline cerebellum and the cerebellar hemispheres. Lesions in each of these regions can result in a different presentation of ataxia. For example, damage to midline cerebellar structures usually presents with gait and truncal ataxia, while damage to the unilateral cerebellar hemisphere usually causes ipsilateral cerebellar ataxia. Understanding this neuroanatomy and correlation to coordination can help with localization. The correlations are listed in **Table 9-1**, although significant clinical overlap exists among them.

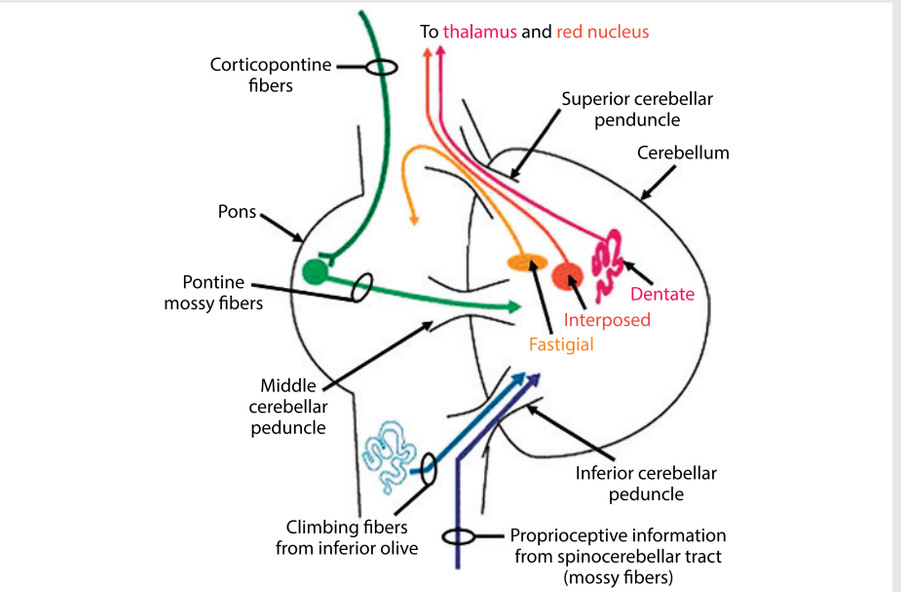

FIGURE 9-1 Afferent and efferent connections of the cerebellum. Main cerebellar afferent connections are by climbing fibers from the inferior olives through the inferior cerebellar peduncles, and pontine mossy fibers through the middle cerebellar peduncles. Cerebellar outputs are from the dentate nucleus and other deep cerebellar nuclei through the superior cerebellar peduncles.

KEY POINT

■ A precise diagnosis of ataxia cannot be based on clinical features alone. Clinical manifestations can be variable, and similar features may not occur in all individuals with a particular disease. For many of the rarer ataxic disorders, the clinical features have been defined on the basis of limited clinical experience.

CLASSIFICATION AND ETIOLOGIES OF ATAXIA

There are different ways to classify ataxias: by age of onset, tempo of onset, and clinical course; anatomic involvement; focal or generalized; or acquired or inherited. Common etiologies (mainly acquired ataxias) are listed in **Table 9-2**, although significant clinical overlap exists among them. Hereditary ataxias are listed separately in **Table 9-3** and **Table 9-4**. Sporadic ataxia remains a temporary diagnosis for adults before a definitive etiology is found. Cases in which all specific diagnoses listed in **Table 9-3** and **Table 9-4** have been ruled out are classified as sporadic adult-onset ataxia of unknown etiology, which still remains a diagnostic challenge.[8]

The list of clinical features is only a rough guide, and a precise diagnosis cannot be based on such features alone. Clinical manifestations can be variable, and the features indicated may not occur in all individuals with a particular disease. For many of the rarer ataxic disorders, the clinical features have been defined on the basis of limited clinical experience.

Hereditary Ataxias

Hereditary ataxias are rare disorders, but are more frequently diagnosed than they were previously as diagnostic technologies are advancing. Hereditary ataxias are classified as autosomal dominant, autosomal recessive, X-linked, or mitochondrial ataxias (**Table 9-3** and **Table 9-4**). The characteristic features may help with recognizing a specific diagnosis.[9–11]

Inherited ataxias, especially autosomal dominant cerebellar ataxias, should be considered when the disease is transmitted vertically from one generation to the next within a family. A documentation of a father-to-son transmission ascertains the autosomal dominant inheritance (**Case 9-1**).

TABLE 9-1 Correlation of Neuroanatomy With Clinical Features of Ataxia

Neuroanatomy	Function	Ataxia or Ataxialike Presentation Arising From Damage of the Region
Cerebellar hemisphere, including dentate nuclei	Integration of sensory input and motor planning for coordination of complex tasks	Ipsilateral limb ataxia, dysdiadochokinesia, dysmetria, intention tremor, and scanning speech
Midline cerebellar structures (vermis, fastigial and interposed nuclei, the vestibulocerebellum, and the paravermis)	Motor execution, rapid and slow eye movements, balance, lower extremity coordination, and vestibular function	Gait ataxia and imbalance, truncal ataxia, dysmetria, ocular findings, head bobbing, and vertigo
Posterior lobe (flocculonodular lobe)	Integration of information from vestibular nuclei	Nystagmus, postural instability, and gait ataxia
Cerebral cortex (frontal lobe)	Planning and initiating gait	Frontal ataxia (Bruns apraxia), magnetic gait (different from ataxic gait), but associated pathology in this region can worsen ataxia
Brainstem (vestibular nuclei, inferior olivary nuclei, pontine nuclei, cerebellar peduncles)	Relay signals in and out of cerebellum	Ataxia associated with cranial nerve dysfunction and motor-sensory deficits
Spinal cord (cuneate fasciculus, gracile fasciculus, and spinocerebellar tracts [mossy fibers])	Conduction of sensory pathways	Sensory ataxia
Musculoskeletal system (gluteal muscles)	Stabilizing the weight-bearing hip	Waddling gait rather than ataxia, but associated pathology in this region can worsen ataxia
Peripheral sensation system and visual system	Proprioception, visual cues	Sensory ataxia with Romberg sign, can worsen cerebellar ataxia
Vestibular system (labyrinth of the inner ear, vestibular nerve, vestibular nuclei)	Sense of balance and special orientation, equilibrium	Disequilibrium, loss of balance associated with dizziness and vertigo, tinnitus and hearing impairment, nystagmus

Spinocerebellar Ataxias

The presence of a family history consistent with autosomal dominant inheritance warrants DNA testing for an SCA, which, in genetic terminology, refers to a group of autosomal dominant disorders with a known chromosomal locus. Primary mitochondrial mutations and X-linked mutations may also be considered depending on the clinical manifestations and family history. With the absence of family history and exclusion of secondary ataxias, sporadic cases may still warrant DNA testing since a negative family history does not exclude inherited disorders and up to 5% of patients with apparently sporadic degenerative ataxia may have positive DNA testing. Because of the cost of DNA testing, health insurance coverage should be taken into consideration. Some clinical features described in **Table 9-3** and **Table 9-4** may provide clues to streamline the DNA testing. While no cure for the SCAs is known, a positive DNA test result provides important practical information to patients and their families. First, it enables patients to plan for the future, such as educational or career decisions, particularly in predictive testing.

TABLE 9-2 Etiologies of Ataxia According to Different Classifications

Classification	Common Etiologies
Time course	Acute (hours to days): Ischemic and hemorrhagic strokes, multiple sclerosis, vestibular neuritis, infections (cerebellitis), parainfectious syndromes, toxic disorders
	Subacute (over weeks): Mass lesions in the posterior fossa; meningeal infiltrates; infections such as human immunodeficiency virus (HIV); Creutzfeldt-Jakob disease; deficiency syndromes such as vitamin B_1 and vitamin B_{12}; hypothyroidism; immune disorders such as paraneoplastic, gluten, and anti–glutamic acid decarboxylase (GAD) ataxia; alcohol
	Chronic (months to years): Mass lesions such as meningiomas, craniovertebral junction anomalies, alcohol, idiopathic/sporadic cerebellar ataxias, hereditary ataxias, neurodegenerative ataxias (Friedreich ataxia, multiple system atrophy–cerebellar type)
	Episodic ataxias: Many inborn errors of metabolism, episodic ataxia syndromes
Distribution	Focal ataxias: Posterior circulation strokes (ischemic, hemorrhagic), primary or metastatic cerebellar tumors, bacterial abscess, progressive multifocal leukoencephalopathy, multiple sclerosis, congenital cyst (Dandy-Walker syndrome)
	Symmetric ataxias: All other systemic, toxic, genetic and neurodegenerative causes of ataxia such as intoxication (alcohol, phenytoin, lithium, barbiturates, toluene, and other chemicals), postinfectious syndrome, paraneoplastic syndrome, ataxia associated with antigliadin antibodies, metabolic disorder, viral cerebellitis, tabes dorsalis, prion disease, hereditary ataxia (autosomal recessive, autosomal dominant, and mitochondrial inherited ataxias)

Second, it provides a basis for genetic counseling for patients and their families. Finally, it allows patients to engage in support group and research activities specific for the genetically defined disease entity. For example, the genotype defined by DNA testing will be in inclusion criteria of most, if not all, future clinical trials of disease-modifying treatments, and once a therapy is developed and approved, patients need to know the genotype of their disease to determine whether the drug is suitable for them.

Sporadic and Idiopathic Adult Ataxias

For older patients presenting with sporadic degenerative ataxia, neurologists should consider the diagnosis of multiple system atrophy–cerebellar type (MSA-C). Documentation of other nervous system involvement, particularly basal ganglia and autonomic dysfunction, is critical for the diagnosis of MSA-C in patients with sporadic ataxia (**Case 9-2**). MRI of the brain may provide a clue to the diagnosis of MSA with brainstem atrophy causing the hot cross bun sign and posterior putaminal hypointensity and a putaminal hyperintense rim on T2*-weighted imaging. The remaining late-onset degenerative ataxias are often referred to as sporadic adult-onset ataxia in the category known as idiopathic late-onset cerebellar ataxia. While these two terms have

TABLE 9-3 Autosomal Dominant Ataxias

Entity	Characteristic Features in Addition to Ataxia	Gene/Mutation
Spinocerebellar ataxia type 1 (SCA1)	Hypermetric saccades, corticospinal tract signs	*ATXN1*/CAG expansion
SCA2	Slow saccades	*ATXN2*/CAG expansion
SCA3 (Machado-Joseph disease)	Bulging eyes, fasciculations, parkinsonism	*ATXN3*/CAG expansion
SCA5	Downbeat nystagmus	*SPTBN2*/deletion, point mutation
SCA6	Downbeat nystagmus	*CACNA1A*/CAG expansion
SCA7	Vision loss due to retinal degeneration	*ATXN7*/CAG expansion
SCA8	Reduced penetrance	*ATXN8*/CTG expansion
SCA10	Seizures	*ATXN10*/ATTCT expansion
SCA11	Downbeat nystagmus	*TTBK2*/deletion
SCA12	Action tremor in midlife	*PPP2R2B*/CAG expansion
SCA13	Developmental disability in childhood onset and a lack of eye movement abnormalities in adult onset (R420)	*KCNC3*/point mutation
SCA14	Tremor, myoclonus, facial myokymia	*PRKCG*/deletion, point mutation
SCA15/SCA16	Postural and kinetic tremor, psychiatric symptoms or dementia	*ITPR1*/duplication
SCA17	Dysarthria before gait ataxia (Huntington disease–like)	*TBP*/CAG expansion
SCA20	Spasmodic dysphonia, palatal tremor	Unknown/point mutation
SCA27	Developmental disability and tremor	*FGF14*/point mutation
SCA34	Tongue atrophy and fasciculations	*AFG3L2*/point mutation
SCA36	Myoclonus, choreoathetosis, dementia (Huntington disease–like)	*NOP56*/ GGCCTG expansion
Dentatorubral-pallidoluysian atrophy	Hyperkeratosis, multiple system atrophy–cerebellar type–like (Huntington disease–like)	*ATN1*/CAG expansion.
Episodic ataxia type 1	Episodic, lasts seconds to minutes, interictal fasciculations	*KCNA1*/point mutation
Episodic ataxia type 2	Episodic, lasts from hours to days, interictal nystagmus	*CACNA1A*/point mutation

TABLE 9-4 Autosomal Recessive Ataxias and Mitochondrial Ataxias

Entity	Features in Addition to Ataxia	Gene/Mutation
Friedreich ataxia	Decreased proprioception, areflexia, square-wave jerks, scoliosis, high-arched feet	*FXN*/GAA expansion
Abetalipoproteinemia	Failure to thrive, steatorrhea	*TTTP*/point mutation
Cayman ataxia	Psychomotor retardation	*MTTP*/point mutation
Ataxia telangiectasia	Telangiectasia in eyes and skin, cancer risk	*ATM*/point mutation
Ataxia with oculomotor apraxia type 1	Oculomotor apraxia	*APTX*/deletion
Ataxia with oculomotor apraxia type 2	Oculomotor apraxia	*SETX*/insertion
Spinocerebellar ataxia with axonal neuropathy type 1	Axonal neuropathy	*TDP1*/point mutation
Autosomal recessive spastic ataxia of Charlevoix-Saguenay	Spasticity, distal muscle atrophy	*SACS*/point mutation
Autosomal recessive cerebellar ataxia type 1	Pure ataxia	*SYNE1*/point mutation
Refsum disease	Retinitis pigmentosa, night blindness	*PAHX, PEX7*/ point mutation
Myoclonic epilepsy, myopathy and sensory ataxia/ataxia neuropathy syndrome	Axonal neuropathy, epilepsy	*POLG*/point mutation
Mitochondrial diseases (including myoclonic epilepsy with ragged red fibers [MERRF]; neuropathy, ataxia, retinitis pigmentosa [NARP] syndrome; mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes [MELAS]; Kearns-Sayre syndrome)	Maternally inherited, myopathy, external ophthalmoplegia, retinal pigmentary degeneration	Point mutation

been used interchangeably, some experts include MSA-C in the category of idiopathic late-onset cerebellar ataxia.

Friedreich Ataxia

Friedreich ataxia is one of the most common genetic autosomal recessive ataxia syndromes. Onset is typically in childhood and young adulthood with progressive ataxia leading to loss of ambulation after 10 to 15 years. Other clinical clues include sensory loss due to dorsal root ganglion and dorsal column degeneration with areflexia and foot deformities, scoliosis, hypertrophic cardiomyopathy, and glucose intolerance.[15] With genetic diagnosis, the phenotype has expanded to include a later presentation (older than 25 years of age up to 60 years of age) and slower progression, which is termed late-onset Friedreich ataxia. Such individuals have retained reflexes, often referred to as Friedreich ataxia with retained reflexes, which may show spasticity with no cardiac or skeletal signs.[16] The disease arises from an abnormal expansion of GAA

Case 9-1

A 44-year-old woman presented with a 6-year history of deteriorating balance. She had begun to use a cane 1 year prior to presentation. She also noted neck spasms. Her father and brother had a similar progressive neurologic disorder. She was of Cuban descent. On examination, she had very slow saccades, normal pursuit eye movements, and no nystagmus. She had pancerebellar ataxia with moderate dysmetria, intention tremor and dysdiadochokinesia in her upper limbs, inability to maintain heel contact to shin, a wide-based gait, inability to perform tandem standing and walking, and scanning speech. Reflexes were absent in her arms and trace in her legs. Cervical dystonia was observed. MRI of the brain showed cerebellar and brainstem atrophy (**Figure 9-2**[12]). DNA testing showed a heterozygous CAG repeat expansion in the *ATXN2* gene.

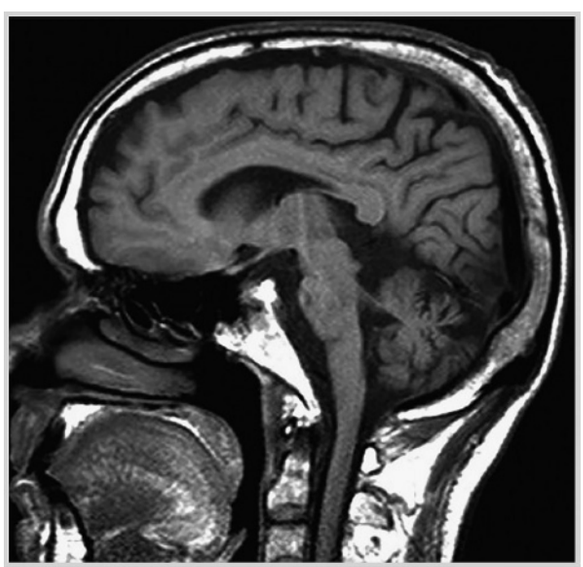

FIGURE 9-2 Sagittal MRI of the patient in Case 9-1 showing atrophy of the cerebellum and brainstem.

Reprinted with permission from Chakor RT, Bharote H, J Postgrad Med.[12] © 2012 Journal of Postgraduate Medicine. *www.jpgmonline.com/article.asp?issn=0022-3859;year=2012;volume=58;issue=4;spage=318;epage=325;aulast=Chakor*.

Comment. The patient's family history indicates an autosomal dominant inheritance pattern. The history of adult-onset ataxia, Cuban descent, and signs characterized by very slow saccades and absent reflexes in addition to cerebellar ataxia is highly suggestive of spinocerebellar ataxia type 2. In this situation, a direct genetic test for spinocerebellar ataxia type 2 rather than a panel is often cost effective.

repeats in the frataxin gene (*FXN*), although point mutations may be present on one of the chromosomes in lieu of the GAA expansion in rare cases. The age of disease onset is inversely correlated with the number of GAA repeats on the smaller allele. Loss of frataxin function in mitochondria leads to iron-sulfur cluster deficits, impaired oxidation, and iron accumulation. Nicotinamide has been shown to increase frataxin but no clinical benefit

Case 9-2

A 71-year-old woman presented for evaluation of an 11-year history of slowly progressive dysarthria and appendicular, gait, and truncal ataxia. At the time of evaluation, the patient walked with a walker and noted urinary urgency and incontinence and frequent diarrhea with fecal incontinence, which she had experienced for the past several years. Urinalysis, urine cultures, and colonoscopy were recently normal. She reported palpitations, excessive drooling, and light-headedness. Family history revealed that her father had been diagnosed with Parkinson disease. She was on a regimen of high-dose coenzyme Q_{10}. Previous neuropsychological testing showed no significant cognitive impairments. On examination, orthostatic hypotension was noted, with a 38 mm Hg drop in systolic blood pressure after standing accompanied by light-headedness. She had scanning dysarthria, irregular ocular pursuit, and nystagmus. Severe appendicular, gait, and truncal ataxia was noted, and she also demonstrated mild cogwheel rigidity and bradykinesia. Brain MRI showed cerebellar and brainstem atrophy with a hot cross bun sign (**Figure 9-3**[13]). She had no response to levodopa treatment. She underwent extensive tests for reversible, treatable etiologies as well as genetic tests for inherited ataxias that were unrevealing.

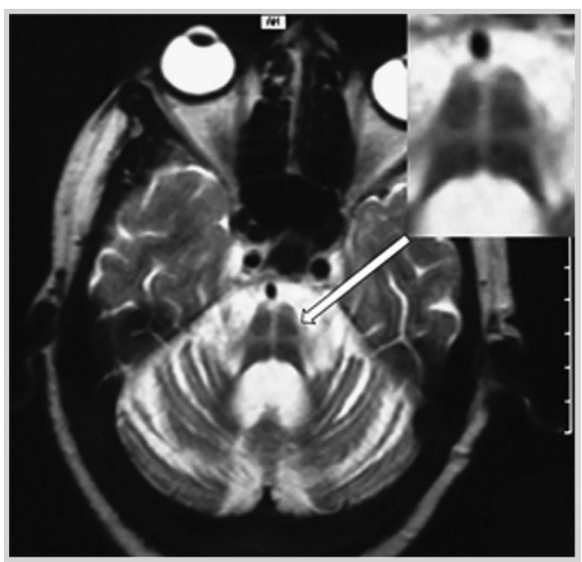

FIGURE 9-3 Axial MRI of the patient in **Case 9-2** showing a hot cross bun sign.

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Comment. This patient has multiple system atrophy (MSA)–cerebellar type, based on the predominant symptom of ataxia. If parkinsonism predominates the presentation, it can be classified as MSA–parkinsonian type.[14] The full features of cerebellar, striatonigral, and autonomic degeneration developed 10 years after the first onset of ataxia. It is often not possible to diagnose MSA at the initial onset of the disorder. A definitive diagnosis can only be made on pathologic findings of glial cytoplasmic inclusions in the central nervous system.

has yet been demonstrated, and studies with the iron chelator deferiprone and the antioxidant idebenone are unclear on long-term benefit. Carbamylated erythropoietin, interferon gamma-1b, pioglitazone, epoetin alfa, and a few other clinical trials have been completed. These studies have not shown convincing evidence of efficacy.[17]

EVALUATION OF THE PATIENT WITH ATAXIA

The history should provide clues to the type of ataxia (eg, cerebellar ataxia, sensory ataxia) or vestibular dysfunction, the affected parts of the body (eg, pancerebellar ataxia, isolated gait ataxia), associated manifestations, and the cause of ataxia. Good history taking will allow neurologists to predict the findings of the physical examination with good accuracy. Detection of any surprising physical findings should warrant revisiting the history.

History

Ataxia may present with a variety of associated signs and symptoms that allow the neurologist to narrow the differential diagnosis. The standard history and physical examination serve as a general framework for the evaluation

of ataxia. As reviewed previously, symptoms include gait disturbance/imbalance, instability with sitting and standing, hand incoordination and intention tremor, slurred speech, loss of sensation, and paresthesia. Symptoms suggesting serious or potentially life-threatening causes include headache, nausea, and vomiting. For functional disability, it is helpful to ask about impairment in activities of daily living and instrumental activities of daily living, such as problems with buttoning clothes or reaching objects and difficulty getting to the bathroom at night.

Age and gender. Cerebellitis is more common in children, and migraine is more common in younger patients, particularly women.

Acute, subacute, or chronic onset. The rate and pattern of the development of ataxia help to narrow the differential diagnosis. Acute-onset ataxia needs special attention as some of the etiologies (eg, stroke) could be life threatening. Gradual onset of ataxia with or without persistent headache or change in mentation may indicate a primary tumor. These symptoms in association with unintentional weight loss may indicate primary or metastatic malignancy. An intermittent pattern to the symptoms may indicate entities such as transient ischemic attack, multiple sclerosis, and inherited episodic ataxia.

Associated symptoms and historical features. Associated symptoms can be clues to localize the lesion and determine the underlying etiology. Symptoms include impairment of consciousness, visual changes, trouble speaking and swallowing, focal sensory loss or weakness, vertigo, slow and abnormal movements, cognitive impairment, and behavior changes. Facial droop, diplopia, pupillary defects, tongue deviation, dysarthria, and dysphonia suggest stroke, tumors, or demyelinating disease. Headache with nausea and vomiting suggests structural lesions in the posterior fossa. Cognitive impairment and hallucinations suggest Wernicke-Korsakoff syndrome, intoxication, or poisoning. If imbalance happens in the dark, sensory ataxia should be considered.

The patient's medication list should be reviewed to determine a possible temporal association between suspected drug use and ataxia onset. Vitamin B_6 (pyridoxine) dosing exceeding 50 mg/d to 100 mg/d may induce neuropathy/neuronopathy, leading to sensory ataxia. Prescription use of anticonvulsants (eg, phenytoin, which may cause ataxia due to either acute toxicity with high doses or chronic use), lithium, or chemotherapeutic agents may indicate drug reaction.

Social history can include questions regarding occupation, possible toxic exposure to chemicals, sexual history (eg, human immunodeficiency virus [HIV], syphilis), drug abuse, and excessive alcohol intake. History of drug or alcohol abuse may indicate solvent or alcohol poisoning or Wernicke encephalopathy. Occupational exposure to heavy metals or solvents may indicate poisoning. Gait disorders that appear to be ataxia with exaggerated and bizarre movements that are inconsistent and incongruous with known ataxia may indicate a nonorganic or functional etiology. However, clinicians should remember that the existence of inconsistency and incongruousness does not necessarily exclude a coexisting organic ataxia. When underlying neurologic causes of ataxia are distorted by psychogenic features, evaluation becomes challenging. Functional ataxia should be a diagnosis of exclusion.

A review of systems should include constitutional symptoms (eg, weight loss, fever, night sweats) and history

of hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation. History of chronic diarrhea may be associated with bismuth abuse and toxicity. Previous history of migraine, visual aura, and triggers for onset of ataxia may indicate migraine as cause. Recent infectious illness may indicate cerebellitis or Miller Fisher syndrome.

Special Considerations on Neurologic Examination of the Patient With Ataxia

Mental status examination. The role of the cerebellum in cognition is increasingly recognized. The cerebellum is not only the site of motor coordination but intimately communicates with the cerebrum for higher cortical functions, including frontal executive functions, spatial orientation, motor memory, language functions, and emotional recognition and production. Patients with cerebellar disorders may exhibit disorders of these cognitive functions, which should be assessed for on examination.

Cranial nerve examination. In various cerebellar disorders, examination of extraocular movements often reveals abnormal pursuit and saccade, ocular dyskinesia such as square-wave jerks, ocular flutter, and opsoclonus. Papilledema may develop with a cerebellar mass lesion, especially with hydrocephalus. Ipsilateral loss of corneal reflex and eighth cranial nerve dysfunction may suggest a cerebellopontine angle tumor. Facial and tongue fasciculations may be a prominent sign of SCA3, and severe tongue atrophy and fasciculations are signs of SCA36.

Vestibular signs. Ataxia from the vestibular system is almost always associated with vertigo and slow nystagmus with or without change of position. Affected patients also tend to veer to the ipsilateral side when they try to walk in a straight line. Hearing loss should be further evaluated to rule out inner ear issues.

Cerebellar signs. The gait is often affected first. Patients cannot stand with feet together. A more sensitive test is tandem stance or walking. Patients tend to veer to the same side. Gait is wide-based with titubation. A focal cerebellar lesion often leads to ipsilateral impaired cerebellar functions, including limb dysmetria, intention tremor, loss of check, hypotonia, and dorsal spooning (hyperextension of interphalangeal joints) of the hand, as well as dysarthria and nystagmus (refer to the previous section on symptoms and signs of ataxia).

Physical examination should give attention not only to appendicular ataxia by examination of limb movements and upright ataxia by examination of stance, gait, and truncal ataxia, but also to ocular dyskinesias, speech abnormalities, proprioceptive loss, and vestibular dysfunction.

Extrapyramidal signs. It is not uncommon for chronic progressive ataxia to be associated with extrapyramidal signs. In hereditary ataxias, extrapyramidal signs are often the indication of spreading of an underlying neurodegenerative process beyond the cerebellum and brainstem. For example, while most SCAs commonly affect gait first, MSA and some SCAs may also have associated parkinsonism. Parkinsonism in SCA2, SCA3, and SCA17 often responds to levodopa; however, when the striatum is involved, patients tend to have parkinsonism and are not responsive to levodopa. While levodopa therapy can induce dyskinesia in these patients treated with levodopa, involuntary movements, including dystonia, may be part of the disease process of SCAs. Careful observation during the examination may be needed to detect them.

KEY POINT

- Physical examination should give attention not only to appendicular ataxia by examination of limb movements and upright ataxia by examination of stance, gait, and truncal ataxia, but also to ocular dyskinesia, speech abnormalities, proprioceptive loss, and vestibular dysfunction.

Strength. It is important to assess whether the degree of ataxia can be explained by muscle weakness. To offset ataxia, the examiner can hold the patient's hands and ask him or her to stand from a sitting position and to stand on toes and heels to examine the functional proximal and distal muscle strength. Symmetric proximal muscle weakness suggests myopathy. Distal muscle weakness suggests generalized neuropathy. Gait dysfunction may also suggest muscle weakness rather than ataxia. For example, when the hip girdle is weak due to myopathy, the pelvis tends to shift toward the side, causing what is called waddling gait, which should not be confused with ataxic gait.

Proprioceptive sensory system. Loss of sensory input from spinocerebellar tracts to the cerebellum may cause sensory ataxia. Any impairment along the proprioceptive pathway may cause sensory loss (for example, Friedreich ataxia, ataxia with vitamin E deficiency, acquired sensory ataxias related to ataxic polyneuropathies [eg, paraneoplastic sensory neuronopathy], Sjögren syndrome, diabetes mellitus, vitamin B_6 toxicity, Miller Fisher syndrome). This can be tested by examining vibration and proprioception at the great toe. The ataxia is usually worsened when taking out the visual cues, in contrast to cerebellar ataxia, where there is no difference in the degree of ataxia with and without eyes closed. Such patients also have trouble standing with feet together and eyes closed (Romberg sign).

Ataxia Evaluation Scales

The International Cooperative Ataxia Rating Scale (ICARS),[18] the Scale for the Assessment and Rating of Ataxia (SARA),[19] and the Friedreich's Ataxia Rating Scale (FARS)[20] were developed for research purposes in inherited ataxias to monitor the natural history and therapeutic response. However, they can also be used in the evaluation of acquired ataxias to help gauge a patient's functional disability and activities of daily living. The Brief Ataxia Rating Scale (BARS)[21] is less time consuming than these rating scales yet captures key ataxia measures and is useful in clinical practice.

DIAGNOSTIC TESTING

The selection of diagnostic tests should be tailored according to the clinical presentation and signs on physical examination.

Laboratory Testing

If drug-induced ataxia is suspected, therapeutic drug levels should be examined. Phenobarbital and butabarbital overdose may occur accidentally or intentionally. The therapeutic range of lithium is narrow, and regular monitoring of blood levels is required. Phenytoin does not follow linear pharmacokinetics and can easily attain supratherapeutic drug concentrations. In the evaluation of acute ataxia in the emergency department, blood alcohol levels should always be tested. A level of 150 mg/dL to 300 mg/dL will almost always affect coordination and balance. Other laboratory tests include vitamin B_6 and vitamin B_{12} levels, thyroid-stimulating hormone (TSH), heavy metal levels (bismuth, lead, mercury), HIV, syphilis, Lyme and toxoplasmosis serology, paraneoplastic panel (including anti-Yo for breast and ovarian cancers, anti-P/Q type voltage-gated calcium channel for lung cancer, anti-Tr for Hodgkin disease, anti-Ri for breast cancer, anti-Hu for lung cancer), and other autoantibodies (anti–glutamic acid decarboxylase [GAD], anti-GQ1b for Miller Fisher syndrome, and anti-gliadin antibody). If hereditary ataxia is suspected, certain laboratory tests can

help narrow down the specific genetic test needed, such as high or low vitamin E and abnormal lipoprotein in abetalipoproteinemia, high α-fetoprotein and low immunoglobulin in ataxia telangiectasia, high serum cholesterol and low albumin in ataxia with oculomotor apraxia type 1, high α-fetoprotein in ataxia with oculomotor apraxia type 2, and high plasma phytanic acid in Refsum disease.

Imaging

Head CT may detect a mass in the posterior cranial fossa and is extensively used in the clinical evaluation of acute stroke, especially for the rapid exclusion of intracerebral hemorrhage. However, head CT may not be ideal for structural lesions in the cerebellum or brainstem because of bone artifacts. For that purpose, brain MRI is more appropriate. Brain MRI is especially useful for ischemic stroke and infratentorial structural lesion evaluation. Noninvasive vascular imaging may also be diagnostically useful, as indicated.

Some MRI signs are diagnostically useful, such as the hot cross bun sign (MSA), middle cerebellar peduncle high signal on T2-weighted images (fragile X tremor-ataxia syndrome [FXTAS]), and molar tooth sign (Joubert syndrome), among others (**Figure 9-2**, **Figure 9-3**, **Figure 9-4**,[22] **Figure 9-5**,[23] **Figure 9-6**,[24] **Figure 9-7**,[25] **Figure 9-8**[26]).

Genetic Testing

For inherited ataxias, genetic tests are available for the CAG expansions involved in SCA1, SCA2, SCA3 (Machado-Joseph disease), SCA6, SCA7, SCA12, SCA17, and dentatorubral-pallidoluysian atrophy; CTG expansion associated with SCA8; GAA expansion in Friedreich ataxia; pentanucleotide

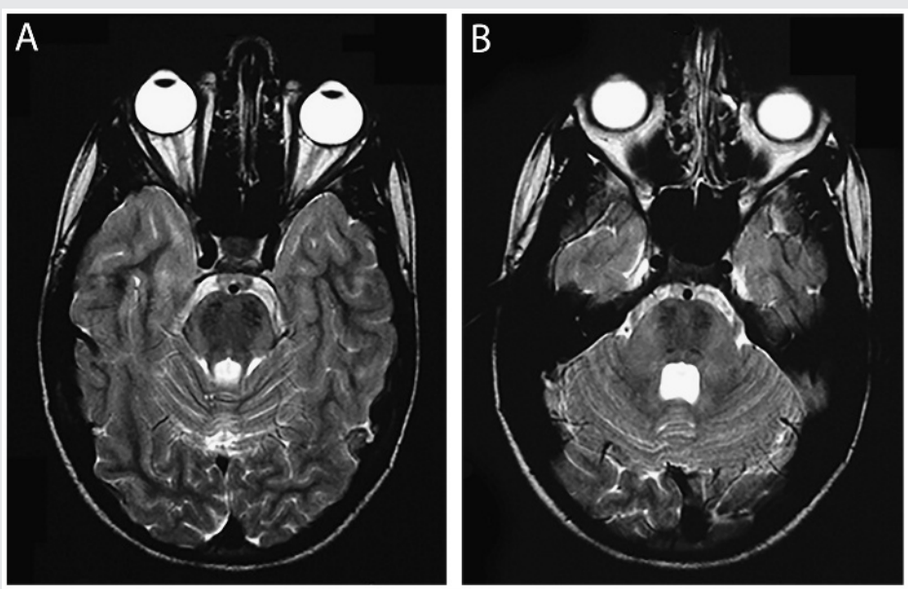

FIGURE 9-4 Axial MRI of a 17-year-old girl with autosomal recessive spastic ataxia of Charlevoix-Saguenay showing degeneration of the corticospinal tract in the brainstem. The patient has had spasticity, ataxia, reduced fine motor function, and abnormal plantar responses since she was 5 years old. The patient's family history was negative except for a cousin with spasticity. Consecutive axial T2-weighted MRI slices (*A, B*) demonstrate linear hypointensity in the pons.

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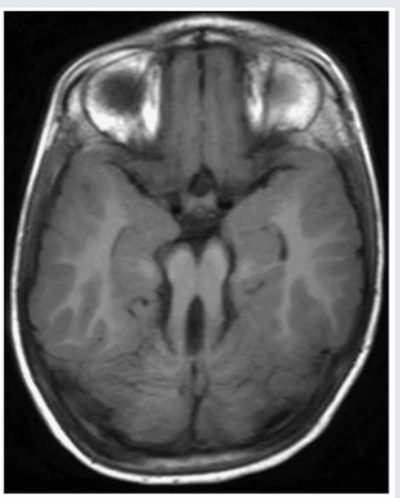

FIGURE 9-5 Joubert syndrome. Axial MRI of a 5-year-old boy with delayed milestones, a prominent forehead and low-set ears, and cerebellar ataxia, hypotonia, and hyperreflexia, showing dysgenesis of the isthmus (the part of the brainstem between the pons and inferior colliculus), thick superior cerebellar peduncles, and hypoplasia of the vermis. These MRI findings produce the molar tooth sign.

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ATTCT repeat expansion in SCA10 and TGGAA repeat expansion in SCA31; hexanucleotide GGCCTG repeat expansion in SCA36; conventional mutations in SCA5, SCA13, SCA14, and episodic ataxia type 2; and mutations in *POLG* (mitochondrial recessive ataxia syndrome), *APTX* (ataxia with oculomotor apraxia type 1), and *SETX* (ataxia with oculomotor apraxia type 2). Other point mutations can also be commercially tested by specific mutation analyses or whole exome sequencing, although interpretation of results beyond the well-characterized disease-causing mutations is challenging (eg, variants of unknown significance). Tests are also commercially available for the common mutations in mitochondrial DNA that may be associated with ataxias such as myoclonic epilepsy with ragged red fibers (MERRF); mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS); and neuropathy, ataxia, retinitis pigmentosa (NARP) syndrome. Many other recently defined gene mutations can be tested for by selected laboratories or research facilities.

Genetic tests are very accurate and becoming less expensive. The choice of tests can be made based on the inheritance pattern, laboratory abnormalities, clinical characteristics, and epidemiologic data. In autosomal dominant and a handful of autosomal recessive ataxias, genetic testing should be done first, and if DNA testing is positive, conventional MRI and blood tests become unnecessary for establishing the diagnosis. For example, if siblings are affected with the typical clinical presentation of Friedreich ataxia **(Supplemental Digital Content 9-2,** *links.lww.com/CONT/A197*), a DNA test should be ordered first. If two GAA expansion alleles are identified, MRI, nerve conduction studies and EMG, and many other tests add only academic footnotes to the diagnosis. These tests would change neither diagnosis nor management unless atypical features suggest concomitant pathology. Similarly, in autosomal dominant disorders with an established genotype in a relative, direct DNA testing should be ordered rather than ordering other laboratory tests or MRI. The website *www.genetests.org* is an excellent resource for information regarding the evolving facts about such tests. A test panel without consideration of clinical features is not encouraged because it is not cost effective. However, if the clinical features are more typical for an inherited ataxia with a negative family history or if the family history is incomplete, the entire dominant ataxia panel should be performed. Whole exome sequencing, whole genome sequencing, and whole

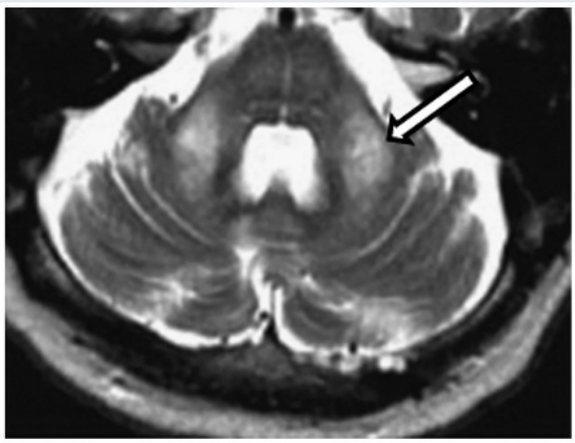

FIGURE 9-6 Fragile X tremor-ataxia syndrome. Axial T2-weighted MRI of a 76-year-old man showing increased signal intensity in the middle cerebellar peduncles. The patient presented to a movement disorders clinic with progressive gait ataxia since the age of 68, with later development of memory problems, occasional confusion, and tremor in his left hand during walking. His family history revealed developmental disability in his grandson through his daughter and premature ovarian failure in one of his granddaughters.

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mitochondrial sequencing are becoming more and more available for idiopathic late-onset cerebellar ataxia and sporadic adult-onset ataxia.[2,27,28] Whole exome sequencing and whole genome sequencing are especially useful in detecting genetic mutations known to cause specific diseases. However, these technologies have technical limitations in diagnosing a repeat expansion disorder. Whole exome sequencing and whole genome sequencing usually generate sequence variants of unknown significance. Advanced bioinformatics, which may be unavailable or costly, would be necessary to analyze the pathogenic significance of these variants, although some research protocols offer thorough whole exome sequencing and whole genome sequencing applications. When sequence analysis is done, polymorphisms of unknown significance may be reported. Such alterations have not been previously reported to be pathogenic. Whether such polymorphisms are truly pathogenic will have to be determined by additional research.

CONCLUSION

Ataxia is a condition that can be easily recognized by the patient's coordination problems, gait disturbance, and trouble speaking. However, the investigation of underlying causes requires systematic evaluation. Other neurologic disorders that can give rise to similar problems with gait and dexterity (eg, nerve and muscle disorders, spinal cord diseases, and basal ganglia diseases) can usually be distinguished on the basis of physical signs alone. In acute settings, the clinician's main mission is to recognize life-threatening events. One common cause of acute ataxia in adults is stroke, which typically happens suddenly with headache, nausea, and vomiting. In nonacute settings,

KEY POINT

- When sequence analysis is done in a patient with ataxia, polymorphisms of unknown significance may be reported. Such alterations have not been previously reported to be pathogenic. Whether such polymorphisms are truly pathogenic will have to be determined by additional research.

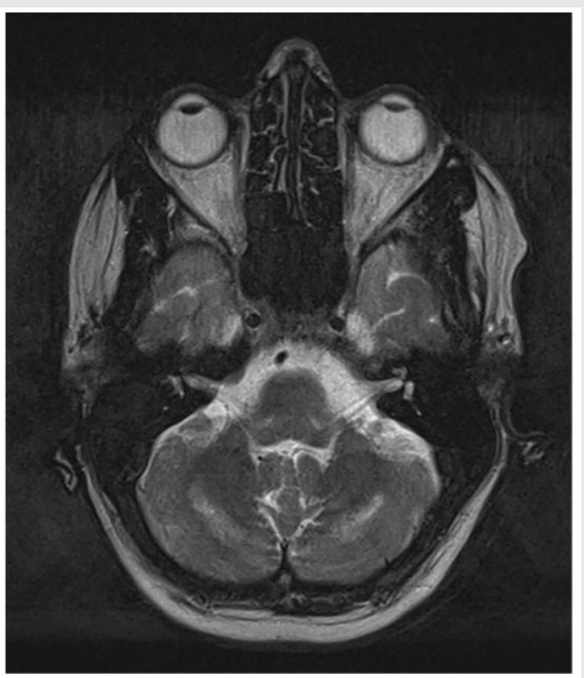

FIGURE 9-7 Sensory ataxic neuropathy with dysarthria and ophthalmoparesis (with *POLG* mutation). Axial T2-weighted MRI of a 50-year-old man with a 4-year history of cerebellar ataxia, numb feet, diplopia, and slurred speech, showing well-defined symmetric signal abnormality in the cerebellar white matter, lateral to and sparing the dentate nuclei.

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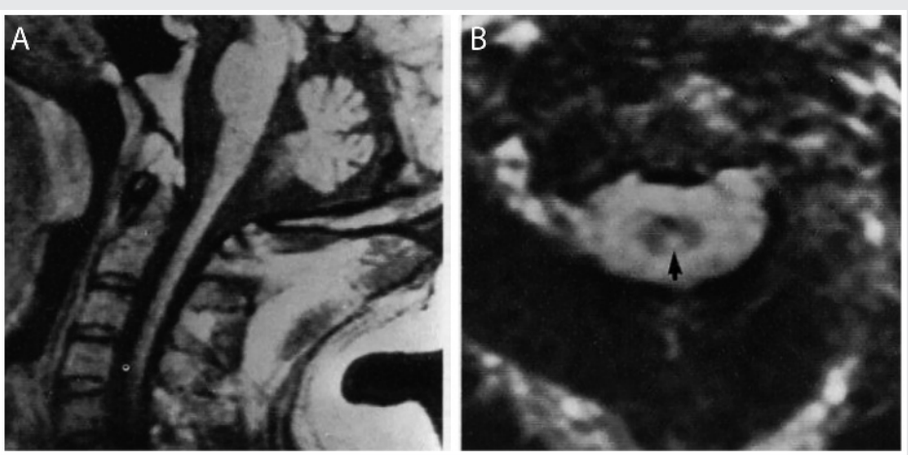

FIGURE 9-8 Atrophy of the cervical spinal cord in a patient with Friedreich ataxia shown on T1-weighted sagittal section (*A*) and T2-weighted horizontal section (*B*) showing the atrophic cervical spinal cord (*arrow*) on MRI.

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no simple algorithm or guideline to follow exists. However, being familiar with ataxia disorders will help physicians solicit related symptoms and diagnostic signs on physical examination, which can often prompt appropriate laboratory and diagnostic tests to confirm a clinical working diagnosis. In certain situations, finding an etiology can become a daunting task. For acquired ataxias, after the offending factor is removed, the disease progression normally stops and the patient will recover in 6 months to a year. With early intervention, especially at a young age, most patients compensate well and will only have very mild incoordination or none at all.

USEFUL WEBSITES

Ataxia Study Group. The Ataxia Study Group carries out clinical trials and other research to identify the causes of ataxia.

www.ataxia-study-group.net

Friedreich's Ataxia Research Alliance. Friedreich's Ataxia Research Alliance is a nonprofit organization engaged in scientific research dedicated to treating and curing Friedreich ataxia.

www.curefa.org

GeneTests. GeneTests provides information on the various disorders and available tests, laboratories, and clinics available for the testing of inherited conditions.

www.genetests.org

National Ataxia Foundation. The National Ataxia Foundation provides information on the diagnosis and causes of ataxia, along with information about support groups, research, and caregiver resources.

www.ataxia.org

Online Mendelian Inheritance in Man (OMIM). OMIM is an online catalog of human genes and genetic disorders containing information on all known mendelian disorders and over 15,000 genes and resources. A search for ataxia links to a large array of genetic resources and research related to various ataxias.

www.omim.org

VIDEO LEGENDS

Supplemental Digital Content 9-1

Early-onset spinocerebellar ataxia type 2. This video shows a girl with slow eye movements and ataxia due to early-onset spinocerebellar ataxia type 2. She also has brisk tendon reflexes (not shown), which is not usual in adult-onset spinocerebellar ataxia type 2.

links.lww.com/CONT/A196

Supplemental Digital Content 9-2

Friedreich ataxia. This video shows a boy with Friedreich ataxia exhibiting gait ataxia, proprioceptive loss, and dysarthria.

links.lww.com/CONT/A197

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