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Ataxia

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Abstract

PURPOSE OF REVIEW: This article reviews the symptoms, laboratory and neuroimaging diagnostic tests, genetics, and management of cerebellar ataxia.

RECENT FINDINGS: Recent advances in genetics have led to the identification of novel genetic causes for ataxia and a more comprehensive understanding of the biological pathways critical for normal cerebellar function. When these molecular pathways become dysfunctional, patients develop cerebellar ataxia. In addition, several ongoing clinical trials for Friedreich ataxia and spinocerebellar ataxia will likely result in novel symptomatic and disease-modifying therapies for ataxia. Antisense oligonucleotides for spinocerebellar ataxias associated with CAG repeat expansions might be a promising therapeutic strategy.

SUMMARY: Cerebellar ataxias include heterogeneous disorders affecting cerebellar function, leading to ataxic symptoms. Step-by-step diagnostic workups with genetic investigations are likely to reveal the underlying causes of ataxia. Some disease-specific therapies for ataxia exist, such as vitamin E for ataxia with vitamin E deficiency and thiamine for Wernicke encephalopathy, highlighting the importance of recognizing these forms of ataxia. Finally, genetic diagnosis for patients with ataxia will accelerate clinical trials for disease-modifying therapy and will have prognostic value and implications for family planning for these patients.

INTRODUCTION

The causes of cerebellar ataxia are diverse, ranging from infectious and immune mediated to degenerative. In addition, many genetic causes of cerebellar ataxia exist. Therefore, the workup for cerebellar ataxia usually poses significant challenges to neurologists. In addition, the treatment for cerebellar ataxia has been traditionally thought to be ineffective, leaving many patients with ataxia untreated. Moreover, nonmotor symptoms, such as depression and mood disorders, are common in patients with ataxia and are often underrecognized and undertreated.

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Kuo discusses the unlabeled/investigational use of amantadine, baclofen, chlorzoxazone, and riluzole for the treatment of cerebellar ataxia; 4-aminopyridine for the treatment of episodic ataxia type 2; deep brain stimulation for the treatment of spinocerebellar ataxia type 2; miglustat for the treatment of Niemann-Pick disease type C; and varenicline for spinocerebellar ataxia type 3.

USEFUL WEBSITES
ONLINE MENDELIAN INHERITANCE IN MAN (OMIM)
The OMIM website provides useful guidance for genetic mutations associated with cerebellar ataxia. omim.org
FRIEDREICH'S ATAXIA RESEARCH ALLIANCE
This website discusses therapy development for Friedreich ataxia. curefa.org/pipeline

To circumvent these challenges of the diagnosis and treatment for patients with ataxia, this review provides step-by-step approaches and an overview for ataxia. This review does not cover ataxia caused by strokes, tumors, or multiple sclerosis since these lesion-related ataxias are easily identified by neuroimaging and are discussed in other issues within the *Continuum* curriculum. The section on ataxia genetics only briefly covers the most common causes of ataxia and does not provide a complete list of ataxic genes, which can be found in other comprehensive reviews.[1–3]

Finally, this article also discusses the medications that have been studied and used to treat ataxia symptoms. This review also highlights important developments in therapies for ataxia, both symptomatic and disease modifying.

SIGNS AND SYMPTOMS OF ATAXIA

Ataxia is a physical finding on examination that is often linked to the disease of the cerebellum. However, abnormal sensory inputs into the cerebellum, such as diseases involving the proprioceptive system/dorsal columns, can also result in ataxia. Hence, ataxia might have both motor and sensory components, and not all patients with ataxia have disease pathology in the cerebellum.

The first step to approaching patients with cerebellar ataxia is to recognize gait imbalance, which is often the first symptom for patients with ataxia.[4] Often, patients will have difficulty going upstairs and downstairs and will have to hold on to the railing. Other common early symptoms include difficulty running, trouble walking in high heels or barefoot on the beach, and veering toward one side. “Do you walk as if you are drunk?” is a useful question, and some patients do show sensitivity to a small amount of ethanol. In the later stage of the disease, frequent falling is frequently encountered. In the early stage, patients with ataxia sometimes have double vision when turning their heads quickly. Blurry vision, resulting from transient and mild double vision, is also common. Slurred speech can develop, making some words difficult to be understood. Patients can also have loss of hand dexterity with bad handwriting and difficulty performing delicate hand tasks.

Once the symptoms of ataxia are established, it is important to further investigate the timing of ataxia development (acute, subacute, chronic, episodic), which will provide important diagnostic clues. TABLE 7-1 lists the common causes for ataxia with different chronicity.

Although recognizing ataxia is an important first step, the associated symptoms in addition to ataxia often can point toward the diagnosis. Therefore, questioning about symptoms of peripheral neuropathy, parkinsonism, sleep dysfunction, autonomic symptoms, seizures, hearing loss, and a family history of ataxia and other balance problems is also an important part of history taking. In addition, a history assessing for toxin and medication exposures will also be helpful in identifying the cause.

NEUROLOGIC EXAMINATION FOR ATAXIA

The neurologic examination of ataxia can be divided into several domains: eyes, speech, hands, legs, and gait.

Several abnormalities of eye movements could be associated with different types of ataxia: (1) saccadic intrusion in fixed gaze (ie, square-wave jerks), which can be seen especially in Friedreich ataxia,[3] (2) horizontal or vertical end-gaze nystagmus, which occurs in many types of ataxia, among which down-beat nystagmus can often been seen in spinocerebellar ataxia (SCA) type 6 (SCA6), (3) hypometric or hypermetric saccades, which can be observed in many types of ataxia, (4) breakdown of smooth pursuit, often encountered in SCA3,[5] (5) slow saccades, typical for SCA2,[5] (6) ophthalmoplegia/ophthalmoparesis, which can be observed in sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO), and (7) ptosis, which can occur in SANDO and ataxia associated with mitochondrial genome mutations.[6] Among these signs, nystagmus and hypometric or hypermetric saccades are commonly shared by ataxic disorders; therefore, these signs are helpful in differentiating cerebellar ataxia from sensory ataxia, especially in the early stages of the disease when no cerebellar atrophy is found on neuroimaging.

Patients with ataxia usually have scanning speech (ie, words are broken up into separate syllables with disrupted normal speech patterns). The speed of speech could become slow, and the volume of speech could be variable.

The three commonly used tasks for ataxic hand examination include (1) finger-nose-finger test (the patient points repeatedly with his or her index finger from his or her nose to the examiner's finger), (2) finger chase (the patient's index finger follows the examiner's moving index finger as precisely as possible), and (3) fast alternating movements (the patient performs cycles of repetitive alternation of pronation and supination of the hand on the thigh). Patients with ataxia will overshoot in the finger-chase test, have intention tremor on the finger-nose-finger test as the tremor becomes more prominent when closer to the target, and have variable rhythm and speed in alternating movements. In heel-to-shin tests, patients with ataxia are asked to straighten one leg and to use the heel of the other leg to slide down the shin from the knee smoothly and precisely but will have difficulty making the heel stay on the shin.

Next, patients should be asked to stand in a natural position so the clinician can observe any truncal sways. Then the patient is instructed, if able to do so, to stand with feet together in the tandem stance, to stand on either foot, or to hop on either foot. These maneuvers are used to test for subtle balance abnormalities associated with cerebellar dysfunction. A useful variation is to ask the patient to close his or her eyes while doing these maneuvers; a considerable worsening in balance during this test will indicate the contribution of sensory neuropathy. Gait examination should focus on the observation of variable stride length and direction, and an ataxic gait might change characteristics at different disease stages. In mild ataxia, the gait might be narrow based but veering toward one direction, and missteps are often observed. Turning can often bring out the gait deficits in patients with ataxia. In moderate ataxia, the gait becomes wide based to compensate for the imbalance. In more advanced ataxia, the stride length can be shortened in addition to a wide-based gait to allow for further compensation. VIDEO 7-1 (links.lww.com/CONT/A358) demonstrates the gait abnormality in different degrees of ataxia. For patients who have difficulty walking upstairs and downstairs or running, observing them performing such tasks usually will yield additional information for the diagnosis.

Once the neurologic examination establishes the presence of ataxia, other associated signs can be critical in pointing toward specific diagnoses. Special attention should be paid to signs of parkinsonism, tremor, dystonia, myoclonus, sensory neuropathy, hyperreflexia, and extensor plantar reflexes. Other signs during the physical examination can possibly aid in diagnosis, including telangiectasia (for ataxia telangiectasia), splenomegaly (for Niemann-Pick disease type C), scoliosis, and pes cavus (for Friedreich ataxia). CASE 7-1 illustrates a case of pathologically confirmed multiple system atrophy with features of cerebellar ataxia and parkinsonism.

LABORATORY TESTS FOR ATAXIA

Serum biomarkers are useful for nutritional and immune-mediated causes of ataxia. Blood levels of vitamin B_{12} and vitamin E can be tested for vitamin deficiency–associated ataxias. Although blood vitamin B_1 levels and associated red blood cell transketolase activity can be measured, it is not clear whether these measurements accurately reflect the brain levels. High clinical suspicion and empiric treatment with thiamine for patients with ataxia with altered mental status and nystagmus are important in treating Wernicke encephalopathy.

Serum antibody levels can indicate specific immune-mediated ataxia (eg, anti–glutamic acid decarboxylase [GAD] antibody). Serum anti–gliadin antibodies and tissue transglutaminase antibodies are associated with ataxia with gluten sensitivity.[7] Anti–thyroperoxidase antibody can indicate ataxia associated with steroid-responsive encephalopathy. Paraneoplastic antibodies should also be examined when encountering patients with subacute cerebellar ataxia. Whether these antibodies are pathogenic for ataxia is still not entirely clear.

Lumbar puncture should be performed in patients with acute or subacute ataxia. CSF analysis for cell counts, glucose, and protein levels, immunoglobulins, and bacterial and viral studies can help identify inflammatory and infectious causes of ataxia. CSF examination can also aid in the diagnosis of Creutzfeldt-Jakob disease.[8] Low CSF glucose levels might indicate ataxia with glucose transporter type 1 deficiency. If acquired causes of cerebellar ataxia have been excluded or if the patient has a family history of ataxia, particularly in first-degree relatives, genetic tests should be ordered, which are detailed below.

NEUROIMAGING FOR ATAXIA

Patients with ataxia should have a brain MRI to identify any structural and vascular lesions, including brain tumors, abscesses, ischemic and hemorrhagic strokes, or multiple sclerosis. Cerebellar atrophy is the most common neuroimaging finding. Neurologists should assess the degree of cerebellar atrophy in the vermis, paravermis, and hemispheric regions (FIGURE 7-1A–D). The foliation of cerebellar lobules becomes obvious as the cerebellum degenerates. The part of the cerebellum that is important for motor control is predominantly located in the anterior lobules, and atrophy in this region is often associated with ataxia. However, atrophy of the posterior lobules of the cerebellum might be related to the nonmotor features of cerebellar dysfunction, such as depression and emotional lability.[9,10] Vermal atrophy might be associated with truncal and gait ataxia whereas paravermal atrophy

might be more related to appendicular ataxia. Some forms of ataxia may not be associated with cerebellar atrophy, especially in the early stage.[3] These ataxias are the result of a predominantly sensory neuropathy, such as Friedreich ataxia and ataxia with vitamin E deficiency, and *POLG* ataxia.

Aside from cerebellar atrophy, other brain MRI findings might indicate specific diagnoses and are listed in TABLE 7-2. The hot cross bun sign (a cross sign in the pons on T2-weighted MRI) can be seen in multiple system atrophy and certain SCAs (FIGURE 7-1E[11]). T2 hyperintensities in the mammillary bodies, periaqueductal gray, and paraventricular thalamus are changes that can be observed in Wernicke encephalopathy. Cerebral white matter changes can be seen in cerebrotendinous xanthomatosis and adult-onset Alexander disease. T2 hyperintensity in the bilateral inferior olivary nucleus, indicating hypertrophic neuronal degeneration, could occur in *POLG* ataxia, adult-onset Alexander disease, and ataxia with gluten sensitivity (FIGURE 7-1F). Other special MRI sequences can be helpful for specific types of ataxia. For instance, the gradient recalled echo sequence (GRE) can be used to identify superficial siderosis (FIGURE 7-1G–H),12 and diffusion-weighted imaging can be useful in diagnosing Creutzfeldt-Jakob disease.[8] Other than the cerebellum, special attention should be paid to the spinal cord because spinal cord atrophy could be seen in patients with Friedreich ataxia (FIGURE 7-1I).

OTHER TESTS FOR ATAXIA

Other associated tests to confirm the extracerebellar symptoms might aid the diagnosis. If multiple system atrophy is suspected, assessment for orthostatic hypotension or urinary disturbance and a sleep study demonstrating rapid eye movement sleep behavior disorder might be necessary. A dopamine transporter scan can be used to determine whether there is presynaptic dopamine terminal loss. Sensory neuropathy could be evaluated by nerve conduction studies. If Creutzfeldt-Jakob disease is in the differential diagnosis, EEG should be performed to look for the typical periodic sharp-wave complexes.

DIAGNOSTIC ALGORITHM FOR ATAXIA

The previous sections covered the history, neurologic examination, and diagnostic tests for cerebellar ataxia. As illustrated in FIGURE 7-2, and using the information mentioned above, the following is a step-by-step algorithm for the evaluation of cerebellar ataxia.

In patients with a balance problem, the first step is to confirm the presence of cerebellar ataxia. Other causes of balance disorders should be considered, including parkinsonism, sensory neuropathy, vestibular problems, muscle weakness, and orthopedic issues. Once ataxia is confirmed, the next step is to assess the acquired causes of ataxia, such as toxin exposures, nutritional deficiency, immune-mediated causes (anti-GAD or ataxia associated with gluten sensitivity), and paraneoplastic causes. Brain MRI should be performed, and variable degrees of cerebellar atrophy should be expected. However, certain forms of cerebellar ataxia with prominent sensory neuronopathy might not have cerebellar atrophy, as mentioned above. Special attention should be paid to specific changes in MRI, as listed in TABLE 7-2.

For patients with a family history of ataxia, the diagnostic flow can be divided into autosomal dominant ataxia, autosomal recessive ataxia, X-linked ataxia, and mitochondrial disorders, depending on the pattern of inheritance. If no family history of ataxia is present and the disease onset occurs when the patient is older than 60 years of age, degenerative causes are likely. In this group, multiple system atrophy is associated with parkinsonism, rapid eye movement sleep behavior disorders, and autonomic dysfunction, whereas idiopathic late-onset cerebellar ataxia usually presents solely as cerebellar ataxia.

GENETICS OF ATAXIA

Genetic causes of ataxia are many. The Online Mendelian Inheritance in Man (OMIM) can serve as a useful resource for up-to-date ataxia genetics.[13] Following is an overview of ataxia genetics based on the pattern of inheritance.

Autosomal Dominant Ataxia

For autosomal dominant cerebellar ataxia, there is designated SCA nomenclature, from type 1 to type 48 to date. Among these, cerebellar ataxia caused by the CAG-repeat expansions, including SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17, are the most common,[14] constituting approximately half of all dominantly inherited ataxias. Other repeat-associated ataxia disorders often have repeat expansions in the noncoding regions of the genes, such as SCA8, SCA10, and SCA12. The rest of the relatively rare SCAs are often associated with the sequence alterations in the coding region.[1] Note that whole exome sequencing is best to detect sequence alterations but not repeat expansions. Therefore, determining repeat expansions in the common SCA genes is the first step for SCA genetics. If no repeat expansions are found, sequencing methods should be the next step.[15]

Each SCA has distinct but overlapping clinical features as listed in TABLE 7-3. Patients with SCA1 have early dysphagia and dysarthria. Patients with SCA2 often have slow saccades, truncal titubation, hyporeflexia, and tremor. Patients with SCA3 commonly have dystonia, depression, restless legs syndrome, and parkinsonism. Patients with SCA6 classically have only cerebellar ataxia without other extracerebellar symptoms. Patients with SCA7 have vision loss due to pigmentary retinal degeneration. Patients with SCA17 have dementia, chorea, and dystonia. Although these clinical symptoms are helpful in pinpointing the correct genetic diagnosis, there is a strong ethnic predilection. For example, SCA2 is very common in Cuba, whereas SCA3 is most common in China, Portugal, and Brazil.[2] Different types of CAG-repeat SCAs have different rates of disease progression. For example, SCA1 progresses most quickly, followed by SCA3 and SCA2. SCA6 has the slowest rate of progression among these subtypes.[16,17] CASE 7-2 and CASE 7-3 demonstrate typical clinical presentations of SCA2 and SCA3, respectively.

The proposed pathomechanism of the common CAG-repeat SCAs is the polyglutamine, and the associated repeats exert toxic effects on the neurons or cause the loss of the normal function of respective proteins.[1] Intraneuronal inclusions can be observed in CAG-repeat SCAs.[24] However, the pathomechanism of SCAs of non–CAG repeats in the noncoding regions is proposed to be primarily due to RNA toxic gain of function. Finally, SCAs

associated with sequence alterations are often due to disturbed protein function from the genetic mutations.[25]

Autosomal Recessive Ataxia

Autosomal recessive ataxia can be divided into three categories: (1) cerebellar ataxia with predominant sensory neuronopathy, (2) cerebellar ataxia with sensorimotor axonal neuropathy, and (3) cerebellar ataxia without sensory neuropathy (TABLE 7-4). Therefore, the characteristics of associated neuropathy are key to the examination in recessive ataxia. The prototypical disease for the category of cerebellar ataxia with predominant sensory neuronopathy is Friedreich ataxia, which is the most common recessive ataxia. Patients with Friedreich ataxia have an age of onset from childhood to the third decade and might also have pes cavus, scoliosis, square-wave jerks, and hyporeflexia. About 15% of Friedreich ataxia cases are adult onset, which could be associated with prominent spasticity and hyperreflexia.[3] Diabetes mellitus and cardiomyopathy are also common in Friedreich ataxia. Friedreich ataxia is caused by intronic GAA repeat expansions of the *FXN* gene, which result in inefficient production of frataxin protein and lead to disturbed mitochondrial function. About 5% of patients with Friedreich ataxia have one allele carrying a point mutation in the *FXN* gene and another allele with repeat expansions. Therefore, a neurologist should still have a high suspicion of Friedreich ataxia if the expanded repeats are detected in only one allele in patients with otherwise classical Friedreich ataxia.

Another relatively common recessive ataxia is SANDO syndrome, caused by *POLG* mutations. The age of onset is in adulthood with ophthalmoplegia, ptosis, myoclonus, and epilepsy.[6] Bilateral inferior olivary nucleus T2 hyperintensity could sometimes be observed on brain MRI (FIGURE 7-1F).

Another group of autosomal recessive ataxias is cerebellar ataxia with sensorimotor axonal neuropathy. Within this group, the common types are ataxia telangiectasia and ataxia with oculomotor apraxia type 1 and type 2. In addition to neuropathy, chorea, dystonia, and spasticity are common symptoms in this group. α-Fetoprotein levels are elevated in ataxia telangiectasia and ataxia with oculomotor apraxia type 2, which sometimes could be used as a screening tool for these diseases. Patients with ataxia telangiectasia have increased risks of cancer and infection, in addition to sensitivity to radiation.

The third category for recessive ataxia is ataxia without sensory neuropathy, among which autosomal recessive cerebellar ataxia type 1 is usually adult onset with upper or lower motor neuron signs, pes cavus, and scoliosis.[26] Patients with Niemann-Pick disease type C have characteristic vertical supranuclear ophthalmoplegia (VIDEO 7-4, links.lww.com/CONT/A361)[27] in addition to mental retardation, dystonia, and cognitive decline.

X-linked Ataxia

The most common X-linked ataxia is fragile X tremor-ataxia syndrome, which is caused by CGG repeat expansions within the *FMR1* gene, leading to RNA toxic function. A longer repeat expansion of the *FMR1* gene, as the result of anticipation, will lead to premature ovarian failure in the patients' daughters and mental retardation in patients' grandsons. Thus, fragile X tremor-ataxia syndrome should be considered in the context of a family history of

mental retardation and premature ovarian failure. Parkinsonism and autonomic dysfunction can also occur; therefore, fragile X tremor-ataxia syndrome should be in the differential diagnosis for multiple system atrophy. T2 hyperintensity in the middle cerebellar peduncles and corpus callosum on brain MRI are characteristics of fragile X tremor-ataxia syndrome and can help with the diagnosis (FIGURE 7-3).[28]

Mitochondrial Ataxia

Mitochondrial DNA mutations can also cause ataxia. The common causes are Kearns-Sayre syndrome, myoclonic epilepsy with ragged red fibers (MERRF), and mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS). Because of the tissue-specific mitochondrial defects (ie, heteroplasmy), muscle biopsy should be performed because mitochondrial defects are more likely to be detected in the non-dividing cells, such as muscles.

Episodic Ataxia

Episodic ataxia (types 1 to 8) constitutes a group of genetic causes for intermittent ataxia attacks, lasting from minutes to days. There might be underlying progressive ataxia in addition to episodic attacks. Some forms of episodic ataxias can be triggered by exertion.[29] The genetic mutations associated with episodic ataxia are often in the ion channels or membrane proteins important to neuronal excitability. Other major differential diagnostic considerations for episodic ataxia are multiple sclerosis and psychogenic ataxia.

A Rational Approach to the Diagnosis of Genetic Ataxia

Despite the rapid advancement of whole exome and genome sequencing technologies, the first approach to the diagnosis of hereditary ataxia is to test for repeat expansions because these repeat-associated ataxias are most common (autosomal dominant: SCA1, SCA2, SCA3, SCA6; autosomal recessive: Friedreich ataxia; X-linked ataxia: fragile X tremor-ataxia syndrome), and repeat-length alterations will not be detected by the sequencing methods. After excluding the repeat-related ataxias, whole exome sequencing can be very useful in determining sequence alterations.[15] Another limitation of whole exome sequencing for ataxia is that this method is not sensitive for large chromosomal deletions or duplications, such as in SCA20, or for ataxia associated with mitochondrial genome mutations, or for repeat expansions in the noncoding regions. A genetic diagnostic test for ataxia should be coupled with the clinical presentation for appropriate genetic tests.

Investigators have performed sequencing analysis in a large cohort of patients with ataxia without a family history. It turns out that autosomal recessive cerebellar ataxia type 1 with *SYNE1* mutation is the most common and, thus, should be kept in mind in adult-onset ataxia with variable motor neuron signs such as hyperreflexia, extensor plantar responses, muscle atrophy, or fasciculations.[15] It has also been recently recognized that genetic mutations for spastic paraplegia can sometimes cause cerebellar ataxia. While these genetic mutations are not traditionally categorized into SCAs or recessive ataxias, clinicians should still keep these genes in mind. One example is the *SPG7* mutation, which has been observed in patients with idiopathic cerebellar ataxia.[30]

DEGENERATIVE ATAXIA

Degenerative forms of ataxia usually occur in patients who are older than 60 years of age and have no family history of ataxia. In this category, multiple system atrophy and idiopathic late-onset cerebellar ataxia are the two most common diseases.

Multiple system atrophy is characterized by cerebellar ataxia, parkinsonism, autonomic instability (orthostatic hypotension; impotence; and urinary frequency, urgency, and incontinence), and pyramidal signs.[31] Depending on the predominant features, multiple system atrophy can also be divided into multiple system atrophy–parkinsonism type or multiple system atrophy–cerebellar type. Multiple system atrophy–cerebellar type constitutes approximately 30% of all multiple system atrophy cases.[31] Patients with multiple system atrophy with predominant cerebellar ataxia generally have a slower disease progression than those with predominant parkinsonism. In the early stage of the disease, patients might present with relatively isolated cerebellar ataxia. Therefore, the history and examination should focus on searching for any signs of parkinsonian features, autonomic dysfunction, and upper motor neuron signs. Rapid eye movement sleep behavior disorder is often present, which can be very helpful in indicating an underlying synucleinopathy associated with multiple system atrophy.[31] Respiratory stridor and obstructive sleep apnea sometimes are present. Therefore, for patients with cerebellar ataxia onset later in life, autonomic tests and sleep studies can provide additional evidence to support the diagnosis of multiple system atrophy when clinical symptoms are not yet evident. Brain MRI in patients with multiple system atrophy may show the hot cross bun sign; this sign might not be evident in the early stage of the disease but can show up later after the disease progresses.

Multiple system atrophy is a disease with a relatively fast progression. However, idiopathic late-onset cerebellar ataxia is a disease with a slow progression, and it usually does not compromise the life span. Patients with idiopathic late-onset cerebellar ataxia usually will not develop other neurologic features such as hyperreflexia or parkinsonism.

Practically, the presence of parkinsonism and autonomic dysfunction in elderly patients with ataxia usually indicates a poor prognosis because the diagnosis is likely to be multiple system atrophy. If no parkinsonism or autonomic dysfunction is seen within 5 years after the onset of ataxia, these patients are likely to follow a benign clinical course with the diagnosis of idiopathic late-onset cerebellar ataxia.

TREATMENT OF ATAXIA

The treatment for ataxia can be divided into symptomatic and disease-modifying therapies. Disease-modifying therapy exists for some causes of ataxia, especially for acquired cases (eg, thiamine for Wernicke encephalopathy,[32] gluten-free diet for ataxia associated with gluten sensitivity, and IV immunoglobulin and plasma exchange for anti-GAD ataxia and paraneoplastic ataxia). Disease-modifying therapies for genetic ataxias include vitamin E replacement for ataxia associated with vitamin E deficiency and abetalipoproteinemia, miglustat for Niemann-Pick disease type C, and ketogenic diet for glucose transporter type 1 deficiency.[33]

There is a pipeline of therapy development for Friedreich ataxia, which includes medications that could improve mitochondrial function and reduce oxidative stress, modulate frataxin-controlled metabolic pathways, serve as frataxin stabilizers or enhancers, or increase *FXN* gene expression.[34] The detailed stages of development in each drug are listed on the Friedreich's Ataxia Research Alliance website.[35]

For symptomatic therapy of cerebellar ataxia, in general, a recently published comprehensive review should be used as a guide.[22] The following are several selectively highlighted commonly used treatment options among ataxia experts. Riluzole 50 mg 2 times a day has been shown to improve dysarthria and gait ataxia[18] and can be tried in patients with ataxia. Monitoring liver function is necessary while patients are treated with riluzole. Varenicline 1 mg 2 times a day has been shown to be helpful in patients with SCA3.[20] The side effect of depression should be closely monitored. 4-Aminopyridine 15 mg/d has been shown to be effective to suppress the number of attacks in patients with episodic ataxia type 2,[36] and it is sometimes useful in treating nystagmus.[37] Other medications, such as amantadine,[38] baclofen, and chloroxazone,[39] can also be used to treat ataxia. Symptoms other than ataxia, such as tremor, dystonia, and depression, should be identified and treated with conventional symptomatic therapy. For instance, postural tremor can be treated with primidone or propranolol, dystonia with botulinum toxin, and depression with antidepressants.

Exercise can provide benefit for patients with ataxia because exercise has been shown to dramatically enhance the life span of SCA1 mouse models.[40] Coordinated training has been demonstrated to provide long-standing benefits for patients with ataxia,[41] and these exercises focus on core strength and balance. Whether aerobic and other forms of exercise also have additional benefits remain to be tested.

Some evidence indicates that dietary supplementation might be helpful in treating ataxia. For example, coenzyme Q10 supplementation might be beneficial for SCAs[21] or multiple system atrophy. Rare mutations of *COQ2*, a gene that encodes an enzyme essential for coenzyme Q10 biosynthesis, have been identified in patients with multiple system atrophy,[42] and patients with idiopathic multiple system atrophy also have decreased brain coenzyme Q10 levels.[43] A clinical trial has been initiated to test MSA-01, a variant of coenzyme Q10 that has more bioavailability to the brain, for patients with multiple system atrophy.[44] Zinc supplementation might also be helpful for patients with SCA2.[19]

The development of ataxia therapy is an exciting area of neurology research. With the advancement of our understanding of cerebellar physiology, ion channel modulation of cerebellar circuitry can present an opportunity for symptomatic therapy for ataxia. Small-conductance calcium-activated potassium channels are enriched within Purkinje cells and can regulate the firing patterns of these neurons. In addition, cerebellar physiology can potentially be modulated by the speed of glutamate uptake in astrocytes. Therefore, medications regulating these mechanisms are currently being tested in patients with genetically confirmed SCA.[45] Deep brain stimulation for patients with ataxia has had variable success, but the most consistent benefit is in tremor of patients with SCA2.[46] Further exploration of new stimulation targets and the stimulation parameters are likely to

identify ways of improving ataxia symptoms. Finally, antisense oligonucleotides have been shown to knock down the toxic protein levels and to improve the symptoms of mouse models of SCA2 and SCA3.[47,48] These studies formulate a strong scientific rationale to test antisense oligonucleotides in patients with ataxia in the near future.

CONCLUSION

The causes of cerebellar ataxia are many and can present as diagnostic challenges. This article provides a step-by-step diagnostic guide for patients with ataxia. The acquired causes of ataxia should first be considered, followed by genetic and degenerative forms of ataxia. If genetic ataxia is suspected, pathologic repeat expansions in the ataxic genes should be determined first, followed by assessing for sequence alterations. Among late-onset cerebellar ataxias, multiple system atrophy is most common and should be considered. Although the treatment for cerebellar ataxia remains only modestly effective, several novel therapies are currently being tested, including pharmacologic therapy, brain stimulation, and antisense oligonucleotides.

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KEY POINTS

- Determining the etiology of cerebellar ataxia is complex; however, step-by-step approaches can streamline the diagnostic workflow.
- Key questions regarding difficulty running, trouble walking in high heels or barefoot on the beach, and veering toward one side can be helpful in identifying the subtle gait abnormality associated with ataxia.
- Patients with ataxia can have a variety of eye movement abnormalities, including nystagmus, hypermetric or hypometric saccades, and ophthalmoplegia.
- The gait abnormality associated with cerebellar ataxia can change over the course of the disease.
- After establishing the signs of cerebellar ataxia, look for other neurologic signs (eg, tremor, dystonia, parkinsonism, motor neuron signs) as clues to the cause of ataxia.
- Laboratory evaluation can be helpful in identifying nutritional and immunologic causes of cerebellar ataxia.
- Aside from cerebellar atrophy, specific changes on MRI associated with different forms of cerebellar ataxia can provide important diagnostic clues.
- The spinocerebellar ataxia nomenclature relates to the autosomal dominant causes of ataxia.
- Autosomal recessive ataxia can be divided into three categories: (1) cerebellar ataxia with predominant sensory neuronopathy, (2) cerebellar ataxia with sensorimotor axonal neuropathy, and (3) cerebellar ataxia without sensory neuropathy.
- Fragile X tremor-ataxia syndrome is the most common cause of X-linked ataxia.
- The first approach to the genetics of ataxia is to investigate for repeat expansions, which are the common causes of autosomal dominant, recessive, and X-linked ataxia.
- Patients with multiple system atrophy can have cerebellar ataxia, parkinsonism, autonomic dysfunction, and pyramidal signs.

CASE 7-1

A 56-year-old woman presented because of imbalance, difficulty walking upstairs and downstairs, and slurred speech that had developed over 4 years.

On examination, she had nystagmus and prominent cerebellar ataxia with finger dysmetria, impaired rapid alternating movements, and inability to perform a tandem walk.

Within 1 year, she had fallen several times and started to use a walker. She also developed two syncopal episodes due to orthostatic hypotension. A repeat neurologic examination revealed marked slowing in hand and leg movements with hypomimic facial expression in addition to worsening of ataxia. Her gait became wide based with a short stride length and no heel strikes (VIDEO 7-2, links.lww.com/CONT/A359). She also fell back ina pull test. Her postmortem pathologic examination demonstrated glial cytoplasmic inclusions, the hallmarks for multiple system atrophy.

COMMENT

This case illustrates a typical presentation of multiple system atrophy, cerebellar type, for which cerebellar ataxia develops first followed by parkinsonism and autonomic features. The symptomatic treatment for such patients should focus on the domain-specific dysfunction (eg, riluzole for ataxia, levodopa for parkinsonism, and management of orthostatic hypotension).

CASE 7-2

A 55-year-old woman presented for evaluation of progressive gait difficulty. She had initially noted difficulty walking downstairs and running at the age of 47. Her imbalance problems became progressively worse over the years, and she developed slurred speech, transient double vision while turning her head quickly, and loss of hand dexterity. She had frequent falls and needed to use a walker. She had an extensive family history of cerebellar ataxia, affecting her mother and brother.

On examination, she had slurred speech and slow saccadic eye movements without nystagmus or hypermetric or hypometric saccades. She had dysmetria on finger-nose-finger tests and overshoot in finger-chase tests. She also had impaired rapid alternating movements. She had a hypomimic facial expression and bradykinesia. Her gait showed variable stride length and was wide based (VIDEO 7-3, links.lww.com/CONT/A360).

Brain MRI showed pontocerebellar atrophy. Genetic tests for repeats revealed pathologic CAG expansions of the *ATXN2* gene of 38 repeats (normal <32), confirming the diagnosis of spinocerebellar ataxia type 2 (SCA2).

The patient was treated with riluzole 50 mg 2 times a day,[18] which provided modest benefits for her speech. Physical therapy helped with her balance. Carbidopa/levodopa 25 mg/100 mg, 3 times a day, improved her parkinsonism by increasing the speed of her movements.

During the follow-up visit, she described depressive symptoms with suicidal ideation. She was treated with duloxetine 30 mg/d, which helped with her mood. She was also treated with zinc 50 mg/d because zinc has been shown to potentially help patients with SCA2.[19]

Five years later, her symptoms progressed, and she needed to use a wheelchair. She had ophthalmoparesis, particularly in vertical gaze, and her saccadic eye movements became very slow (VIDEO 7-3, links.lww.com/CONT/A360).

COMMENT

This case demonstrates that determination for repeat expansions is the first step for autosomal dominant ataxia. Slow saccades are the key feature for SCA2. Other than treating ataxia symptoms, parkinsonism in patients with ataxia can sometimes respond to carbidopa/levodopa. Finally, depressive symptoms are very common in patients with cerebellar ataxia,[9] possibly due to the cerebellar cognitive affective syndrome,[10] and should be treated with antidepressants.

CASE 7-3

A 49-year-old man presented for evaluation of a 5-year history of progressive slowness of movements, decreased facial expression, and shuffling gait. Further questioning revealed that his sister also had an imbalance problem, which had started at 36 years of age.

On examination, he had a hypomimic facial expression, bradykinesia, a parkinsonian gait, and mild cerebellar ataxia with a variable step length. The neurologic examination of his sister, at the age of 51, showed prominent cerebellar ataxia. Both the patient's and his sister's brain MRI showed pontocerebellar atrophy. The patient's dopamine transporter scan showed decreased uptake in the bilateral striatum.

He was treated with carbidopa/levodopa up to 25 mg/250 mg 3 times a day, which significantly improved his symptoms. The patient's genetic test for repeat expansions revealed pathologic expansions of 73 in *ATXN3* (normal <50). He later developed painful peripheral neuropathy in his legs, and his cerebellar ataxia became more prominent. He also had depressive symptoms and felt hopeless and helpless.

In addition to levodopa, the patient was also prescribed varenicline 1 mg 2 times a day,[20] which improved his gait to a modest degree. He was treated with 2000 mg/d of coenzyme Q10 based on retrospective data.[21] His depression was treated with citalopram 20 mg/d.

COMMENT

This case exemplifies the clinical heterogeneity of monogenic ataxia, ranging from levodopa-responsive parkinsonism to peripheral neuropathy and cerebellar ataxia. Spinocerebellar ataxias (SCAs) should be in the differential diagnosis of young-onset parkinsonism. Although the majority of the treatment options for SCAs lack large-scale randomized controlled clinical trials, neurologists still should try different therapies based on published data.[22] For example, citalopram has been shown to decrease ataxin-3 aggregation in animal models of SCA3[23]; thus, it might provide additional benefits to patients with SCA3.

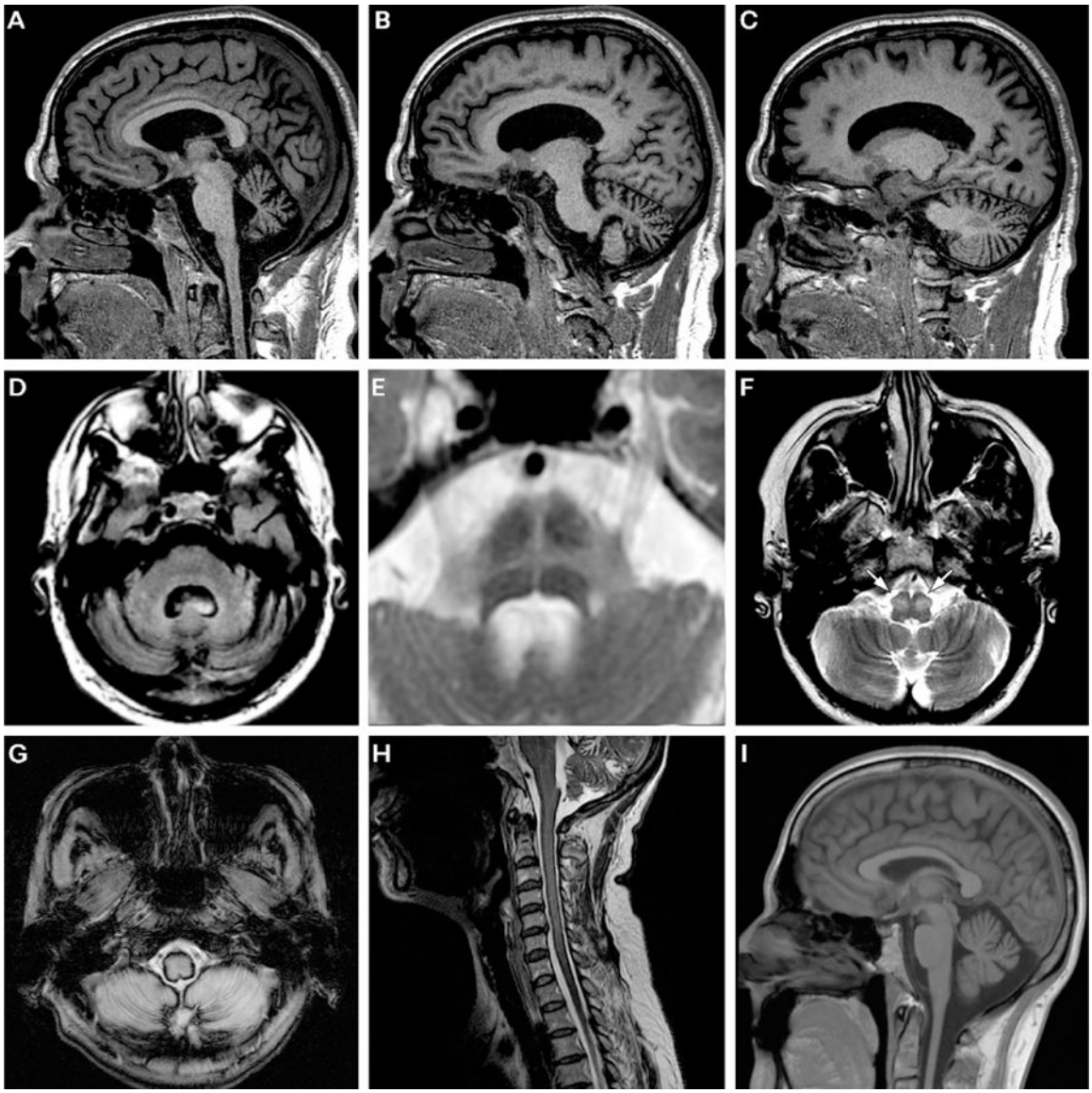

FIGURE 7-1.

Sagittal T1-weighted brain MRI demonstrates cerebellar atrophy in a patient with spinocerebellar ataxia type 13. Note that prominent cerebellar foliation and sulci are seen in the cerebellar vermis (*A*), paravermis (*B*), and cerebellar hemisphere (*C*). Prominent cerebellar sulci are also noted in the axial fluid-attenuated inversion recovery (FLAIR) sequence in the same patient (*D*). Axial T2-weighted MRI sequence shows the hot cross bun sign in the pons of a patient with multiple system atrophy (*E*). Axial T2-weighted brain MRI demonstrates hyperintensities in the bilateral inferior olivary nuclei (*F, arrows*) in a patient with *POLG* ataxia. Axial gradient recalled echo (GRE) brain (*G*) and sagittal spinal cord MRI (*H*) demonstrated hypointensity surrounding the brainstem, cerebellum, and spinal cord in a patient with superficial siderosis. Sagittal T1-weighted brain MRI shows spinal cord atrophy but no cerebellar atrophy in a patient with Friedreich ataxia (*I*).

Panel E is reprinted with permission from McFarland NR, Continuum (Minneap Minn).[11] © 2016 American Academy of Neurology.

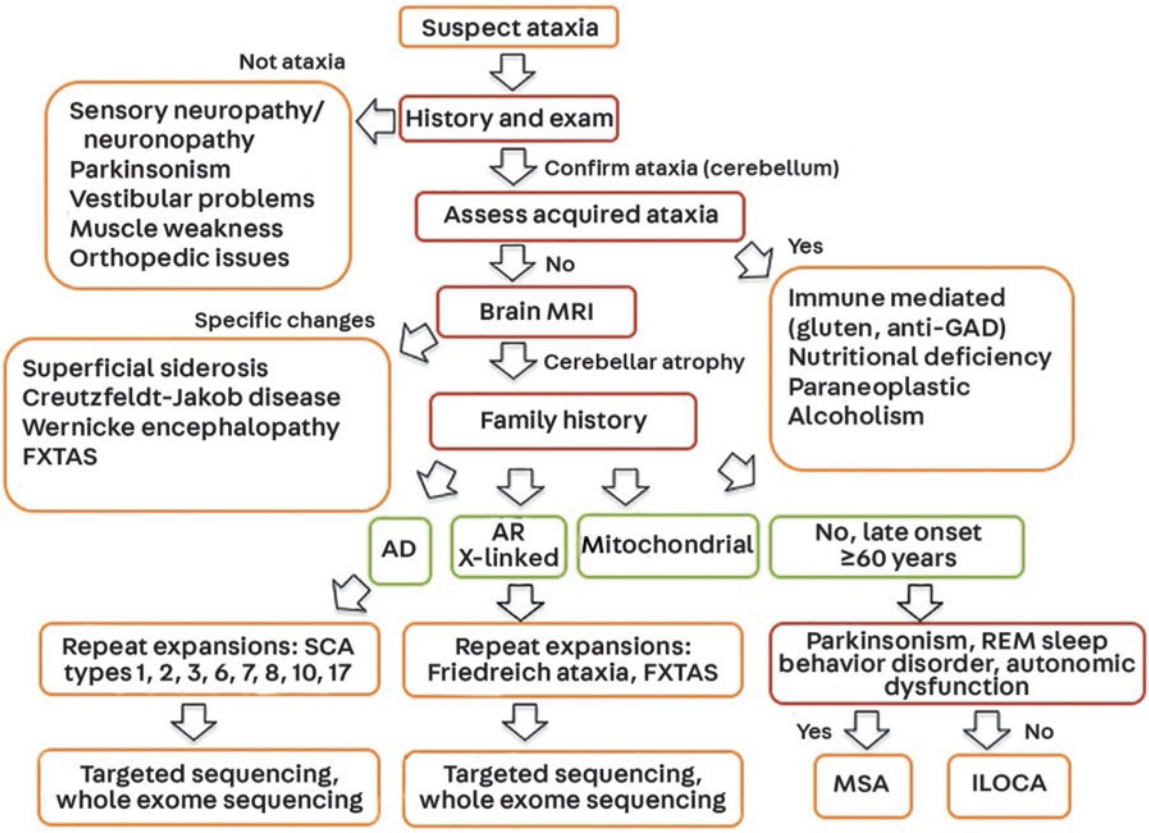

FIGURE 7-2.

The diagnostic workflow for cerebellar ataxia.

AD = autosomal dominant; AR = autosomal recessive; FXTAS = fragile X tremor-ataxia syndrome; GAD = glutamic acid decarboxylase; ILOCA = idiopathic late-onset cerebellar ataxia; MRI = magnetic resonance imaging; MSA = multiple system atrophy; REM = rapid eye movement; SCA = spinocerebellar ataxia.

FIGURE 7-3.
Fragile X tremor-ataxia syndrome. Axial T2-weighted MRI of a 76-year-old man with fragile X tremor-ataxia syndrome showing symmetric increased signal within the middle cerebellar peduncles (*arrow*).
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VIDEO 7-1. Different degrees of gait ataxia.

The first video segment shows an 18-year-old man with ataxia with oculomotor apraxia type 2. Mild gait ataxia can manifest with variable step length, side steps, and veering toward one side without a marked wide base. The second video segment shows a 37-year-old man with idiopathic cerebellar ataxia. In patients with moderate ataxia, the gait becomes wide based with obvious variable stride lengths. The third video segment shows a 32-year-old woman with spinocerebellar ataxia type 2. In the advanced stages of ataxia, a wide-based gait is more evident, and the stride length becomes shorter to compensate for ataxia.

links.lww.com/CONT/A358

VIDEO 7-2. Multiple system atrophy, cerebellar type.

Video shows the 56-year-old woman discussed in CASE 7-1 who developed imbalance and walked “as if she were drunk.” She veered toward one side while walking, had two episodes of syncope, and her speech and hand dexterity were subsequently involved. On examination, she has hypomimic facial expression, hypermetric saccades, dysmetria on finger-nose-finger tests, bradykinesia in finger taps, and ataxic gait with variable footsteps. Her postmortem brain pathology demonstrated glial cytoplasmic inclusions along with olivopontocerebellar atrophy, confirming the diagnosis of multiple system atrophy, cerebellar type.

links.lww.com/CONT/A359

VIDEO 7-3. Spinocerebellar ataxia type 2.

The first video segment shows the 55-year-old woman discussed in CASE 7-2 with spinocerebellar ataxia type 2. She has limited upward gaze and slow saccadic eye movements without nystagmus or hypermetric or hypometric saccades. She has dysmetria on finger nose-finger tests and an overshoot in finger chase tests. She also has impaired rapid alternating movements. Her facial expression is hypomimic, and her gait is wide based and shows variable stride length. The second video segment shows the same patient 5 years later. Her symptoms have progressed. She has ophthalmoparesis, particularly in vertical gaze, and her saccadic eye movements have become very slow.

links.lww.com/CONT/A360

VIDEO 7-4. Niemann-Pick disease type C.

Video shows a 30-year-old man with Niemann-Pick disease type C. He has relatively preserved smooth pursuit in the horizontal direction without end-gaze nystagmus. He can perform upward pursuit, but his downward pursuit movements are extremely slow. He also has relatively preserved horizontal saccades and has great difficulty in vertical saccades, particularly in the downward direction.

links.lww.com/CONT/A361

TABLE 7-1

Acute, Subacute, Chronic, and Episodic Causes of Cerebellar Ataxia

Acute Causes of Cerebellar Ataxia (Minutes to a Few Days)
◆ Vascular causes: ischemic or hemorrhagic cerebellar strokes
◆ Ethanol intoxication
◆ Toxins (mercury, thallium, toluene, solvents)
◆ Medication (phenytoin, carbamazepine, phenobarbital, lithium)
◆ Multiple sclerosis
◆ Meningitis, particularly basilar meningitis
◆ Viral cerebellitis
◆ Cerebellar abscess
◆ Wernicke encephalopathy/thiamine deficiency
Subacute Causes of Cerebellar Ataxia (Weeks to Months)
◆ Paraneoplastic cerebellar degeneration
◆ Brain tumors
◆ Creutzfeldt-Jakob disease
◆ Superficial siderosis
◆ Anti–glutamic acid decarboxylase ataxia
Chronic Causes of Cerebellar Ataxia (Months to Years)
◆ Ataxia associated with gluten sensitivity
◆ Genetic ataxia
◆ Mitochondrial disease
◆ Multiple system atrophy
◆ Idiopathic late-onset cerebellar ataxia
Episodic Causes of Cerebellar Ataxia
◆ Genetic episodic ataxia
◆ Psychogenic ataxia
◆ Mitochondrial disease
◆ Multiple sclerosis

TABLE 7-2

Brain MRI Findings Associated With Specific Forms of Ataxia

Brain MRI Findings	Associated Findings and Pathology	Associated Ataxia
No cerebellar atrophy	No obvious structural cerebellar cortical degeneration	Friedreich ataxia, ataxia with vitamin E deficiency, abetalipoproteinemia, immune-mediated ataxia
Hot cross bun sign	Pontine atrophy	Multiple system atrophy, spinocerebellar ataxia type 2
Cervical spinal cord atrophy	Cervical spinal cord atrophy	Friedreich ataxia
T2 hyperintensity in the middle cerebellar peduncles	Degeneration/demyelination of middle cerebellar peduncles	Multiple system atrophy, fragile X tremor-ataxia syndrome
T2 hyperintensity in the mammillary bodies, periaqueductal gray, and paraventricular thalamus	Possibly petechial hemorrhages in these brain regions	Wernicke encephalopathy
T2 hyperintensity in the bilateral inferior olivary nuclei	Hypertrophic degeneration of the neurons in the inferior olivary nuclei	*POLG* ataxia, adult-onset Alexander disease, ataxia with gluten sensitivity
Dentate nucleus calcification (CT)[a]	Dentate nucleus calcification	Spinocerebellar ataxia type 20
T2 hyperintensity in the white matter	Leukoencephalopathy	Cerebrotendinous xanthomatosis, adult-onset Alexander disease
Medullary atrophy	Medullary atrophy	Adult-onset Alexander disease
T2 gradient recalled echo showing linear hypointensity around the cerebellum and brainstem	Iron deposition on the surface of the brain parenchyma	Superficial siderosis
Diffusion-weighted imaging hyperintensity in the cerebral cortex, basal ganglia, or thalamus	Spongiform degeneration	Creutzfeldt-Jakob disease

CT = computed tomography; MRI = magnetic resonance imaging.

[a]This particular finding is best seen on the CT scan.

TABLE 7-3

Common Autosomal Dominant Ataxias Associated With Repeat Expansions

Disease	Gene Alterations	Associated Clinical Features and Notes
SCA1	CAG repeats in *ATXN1*	Dysphagia, dysarthria, pyramidal signs
SCA2	CAG repeats in *ATXN2*	Slow saccades, truncal sways, hyporeflexia, postural and rest tremor, parkinsonism
SCA3	CAG repeats in *ATXN3*	Abnormal smooth pursuit, depression, restless legs syndrome, dystonia, parkinsonism
SCA6	CAG repeats in *CACNA1A*	Pure cerebellar ataxia
SCA7	CAG repeats in *ATXN7*	Vision loss/pigmentary retinal degeneration
SCA8	CTG repeats in *ATXN8* and *ATXN8OS*	Hyperreflexia
SCA10	ATTCT repeats in *ATXN10*	Epilepsy
SCA17	CAG repeats in *TBP*	Dementia, chorea, dystonia

SCA = spinocerebellar ataxia.

TABLE 7-4

Common Causes of Autosomal Recessive Ataxia

Disease	Genetic Mutations	Age at Onset	Associated Clinical Features
Cerebellar Ataxia With Predominant Sensory Neuronopathy			
Friedreich ataxia	Repeat expansions in intron 1 of *FXN* gene	From childhood to third decade	Pes cavus, scoliosis, square-wave jerks, hyporeflexia, spasticity (adult onset)
Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO)	*POLG* mutations	20–60 years	Ophthalmoplegia, dysarthria, ptosis, myoclonus, epilepsy
Cerebellar Ataxia With Sensorimotor Axonal Neuropathy			
Ataxia telangiectasia	*ATM* mutations	<5 years	Telangiectasia, chorea, dystonia, susceptibility to infections and cancer, radiosensitivity, elevated ?-fetoprotein
Ataxia with oculomotor apraxia type 1	*APTX* mutations	<20 years	Oculomotor apraxia, chorea, dystonia
Ataxia with oculomotor apraxia type 2	*SETX* mutations	From childhood to third decade	Oculomotor apraxia, chorea, dystonia, elevated ?-fetoprotein
Cerebrotendinous xanthomatosis	*CYP27* mutations	Childhood	Spasticity, mental retardation, tendon xanthoma, chronic diarrhea, premature cataract
Cerebellar Ataxia Without Sensory Neuropathy			
Autosomal recessive cerebellar ataxia type 1	*SYNE1* mutations	From second to fifth decade	Spasticity, lower motor neuron signs
Autosomal recessive cerebellar ataxia type 2	*ADCK3* mutations	<10 years	Mental retardation, myoclonus, epilepsy, exercise intolerance
Niemann-Pick disease type C	*NPC1* and *NPC2* mutations	From first to third decade	Vertical supranuclear ophthalmoplegia, splenomegaly, dystonia, cognitive decline