

CEREBELLAR DISORDERS AND SPINOCEREBELLAR ATAXIA

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ABSTRACT

Cerebellar disorders have a variety of inherited and sporadic causes. Advances in genetics have led to the successful classification of over 20 forms of autosomal dominant and recessive cerebellar ataxias with variable phenotypes and have shed light on the underlying pathophysiology of many of these disorders. Successful disease-modifying or symptomatic treatments for these conditions, however, have remained limited.

DEFINITION

The principal function of the cerebellum is the modulation of movement. Patients with cerebellar disorders manifest movement that is not fluid but is composed of fragmented movements that are inaccurate in velocity, direction, timing, and amplitude. Such abnormalities of movement in cerebellar disorders include ataxia, dysmetria, and dysdiadochokinesia. The ataxic patient ambulates with a wide-based stance and gait, where the legs may be hyperextended at the knee and the stride is irregular in length and cadence. Dysmetria can be defined as an abnormality in force and magnitude of movement and is typically uncovered on neurologic examination by finger-to-nose testing where the limb either passes or falls short of the target. Dysdiadochokinesia is an inability to perform rapid alternating movements in a rhythmic, fluid fashion. A high-amplitude proximal limb intention tremor, where the oscillation of the amplitude increases near the target or endpoint of movement, may also accompany the

other movement abnormalities in cerebellar diseases. Hypotonia, scanning dysarthria, nystagmus, and ocular dysmetria are other manifestations found in subjects with cerebellar dysfunction (Gilman, 1997).

Clinical Features and Classifications

Disorders of the cerebellum are best divided into inherited and acquired or sporadic forms of disease. The autosomal dominant cerebellar ataxias (ADCAs) were previously classified by phenotypic expression (Harding, 1995). ADCA-1 presented with cerebellar ataxia and a combination of pyramidal, neuropathic, and extrapyramidal signs. ADCA-2 presented with cerebellar ataxia and retinal degeneration. ADCA-3 presented with pure cerebellar ataxia (Harding, 1995). Recent advances in genetics have led to a detailed and lengthy list of autosomal dominant and recessive forms of disease, which previously defied classification due to tremendous phenotypic variability among members of the same kindred.

Autosomal Dominant Spinocerebellar Ataxias

Spinocerebellar ataxia type 1 (Table 9-1). Spinocerebellar ataxia (SCA) type 1 (SCA1) is characterized by the presence of gait and limb ataxia, nystagmus, dysarthria, pyramidal tract signs, polyneuropathy, and in

the later stages of the disease ophthalmoplegia, extrapyramidal signs, and other bulbar signs such as tongue atrophy and facial fasciculations. Typical age of onset of symptoms is in the third or fourth decade. The responsible gene mutation is an expanded CAG repeat on chromosome 6p22-p23. Normal

TABLE 9-1 Summary of Autosomal Dominant Inherited Ataxias

| Disorder | Chromosome | Mutation | Distinguishing Features | Age of Onset (Median and/or Range) |
|----------|------------|---------------------------|--|---|
| SCA1 | 6 | CAG repeat | Pyramidal tract signs, polyneuropathy, ophthalmoplegia, extrapyramidal signs | Third to fourth decade |
| SCA2 | 12 | CAG repeat | Early slow saccades and ophthalmoplegia Myoclonus, polyneuropathy, dementia | Third to fourth decade |
| SCA3/MJD | 14 | CAG repeat | Extrapyramidal signs, amyotrophy, bulging eyes, ophthalmoplegia | Third to fourth decade (childhood to 60s) |
| SCA4 | 16 | Unknown | Axonal sensory polyneuropathy | 39 years |
| SCA5 | 11 | Unknown | Pure cerebellar syndrome, benign course | Third to fourth decades (10 to 68 years) |
| SCA6 | 19 | CAG repeat | Usually pure cerebellar syndrome, may be initially episodic, late onset | Sixth decade |
| SCA7 | 3 | CAG repeat | Optic atrophy, pigmented retinopathy, extreme anticipation | 2 to 65 years |
| SCA8 | 13 | CTC repeat untranslated | Spasticity, impaired vibratory sense, early dysarthria | 13 to 65 years |
| SCA10 | 22 | ATTCT repeat untranslated | Seizures | Third to fourth decades |
| SCA11 | 15 | Unknown | Mainly cerebellar signs, benign course, hyperreflexia | 25 years |
| SCA12 | 5 | CAG repeat untranslated | Upper extremity and head tremor, dementia in advanced stages | 8 to 55 years |

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TABLE 9-1 *Continued*

| Disorder | Chromosome | Mutation | Distinguishing Features | Age of Onset (Median and/or Range) |
|-------------------|------------|-------------------|---|------------------------------------|
| SCA13 | 19 | Unknown | Mental retardation, psychomotor developmental delay | Early childhood |
| SCA14 | 19 | Unknown | Axial myoclonus and tremor | 12 to 42 years |
| SCA15 (tentative) | Unknown | Unknown | Pure cerebellar syndrome | Childhood to middle age |
| SCA16 | 8 | Unknown | Pure cerebellar syndrome, rare head tremor | 20 to 66 years |
| SCA17 | 6 | CAG/CAA repeat | Late dementia, bradykinesia, and hyperreflexia | Third decade |
| SCA19 | 1 | Unknown | Myoclonus, cognitive impairment, irregular postural tremor | 20 to 45 years |
| SCA21 | 7 | Unknown | Extrapyramidal signs, hyporeflexia, cognitive impairment | 17 years (6 to 30 years) |
| DRPLA | 12 | CAG repeat | Myoclonus, epilepsy, chorea, dystonia, dementia, and parkinsonism | Childhood to adulthood |
| EA-1 | 12 | Missense | Interictal myokymia | Late childhood |
| EA-2 | 19 | Point or missense | Interictal nystagmus, vertigo | Childhood or adolescence |

SCA = spinocerebellar ataxia; MJD = Machado-Joseph disease; DRPLA = dentatorubral-pallidoluysian atrophy; EA = episodic ataxia.

Adapted from the following sources:

Bird T. Ataxia overview. Gene reviews. Available at www.genereviews.org. Accessed February 25, 2004.
 Subramony SH, Nance M. Diagnosis and management of the inherited ataxias. *Neurologist* 1998;4:327-338.
 Evidente VG, Gwinn-Hardy KA, Caviness JN, Gilman S. Hereditary ataxias. *Mayo Clin Proc* 2000;75:475-490.

alleles contain 19 to 36 CAG repeats, and expanded alleles have 42 to 82 repeats. The age of onset and severity of disease correlate with the length of the CAG expansion, where the longer expansion produces an earlier onset and more severe disease presentation. Anticipation is evident in successive generations, resulting from amplification of the CAG repeat during transmission from parent to offspring (Evidente et al, 2000; Paulson and Ammache, 2001; Subramony and Nance, 1998).

Spinocerebellar ataxia type 2. SCA2 may be phenotypically similar to SCA1 with progressive gait and limb ataxia and dysarthria. Nystagmus is not usually seen due to the early presence of extremely slow saccades and ophthalmoplegia. Corticospinal tract involvement is less common than in SCA1, and peripheral nerve involvement is often present early, with atrophy, areflexia, and fasciculations noted. Myoclonus and postural and kinetic tremors are also seen. Dementia may

result in the later stages, and extrapyramidal signs including choreoathetosis and parkinsonism may also evolve later in the disease. In fact, several cases have been described in which the SCA2 genotype presented as a seemingly typical case of familial dopa-responsive parkinsonism (Lu et al, 2002). The mean age of onset is in the third and fourth decades. The SCA2 mutation is an expanded CAG repeat in the ataxin-2 gene on chromosome 12q23-q24. Normal alleles have 14 to 31 CAG repeats, and mutated alleles have 34 to 79 CAG repeats. The function of the ataxin-2 protein remains unknown (Evidente et al, 2000; Paulson and Ammache, 2001; Subramony and Nance, 1998).

Spinocerebellar ataxia type 3. SCA3, also known as Machado-Joseph's disease (MJD), is the most common autosomal dominant inherited ataxia in the United States. SCA3 presents with progressive gait and limb ataxia and a variable combination of other neurologic signs including peripheral neuropathy, amyotrophy, spasticity, bradykinesia, rigidity, dystonia, supranuclear ophthalmoplegia and bulging eyes, dysarthria, dysphagia, tongue atrophy, facial fasciculations, and proprioceptive sensory loss (**Case 9-1**). Because of the tremendous variability in phenotypic presentation, SCA3/MJD is often subdivided into four separate phenotypes: type 1 manifests with a spastic-rigid syndrome often associated with bradykinesia and dystonia and has an earlier age of onset and more aggressive course; type 2 manifests as a spastic ataxia; type 3 presents with a later age of onset and a milder form of ataxia but prominent peripheral neuropathy and amyotrophy (Sequeiros and Coutinho, 1993); and type 4 has a predominantly parkinsonian presentation that may be dopa responsive. The mean age of onset is in the 30s or 40s, but the age range is broad, from

childhood to the 60s. The SCA3/MJD mutation is an expanded CAG repeat in the gene for ataxin-3 on chromosome 14q24-q32. Normal alleles contain 12 to 40 trinucleotide repeats, while expanded alleles contain 56 to 200 or more repeats. As with other trinucleotide repeat diseases, age of onset (inversely) and disease severity correlate with CAG repeat length, and anticipation is seen (Evidente et al, 2000; Paulson and Ammache, 2001; Subramony and Nance, 1998). Intermediate repeat lengths of 53 and 54 have been reported to produce an abnormal phenotype. SCA3/MJD mutations may also have an association with restless legs syndrome (van Alfen et al, 2001) (**Case 9-2**).

Spinocerebellar ataxia type 4. SCA4 presents with a progressive gait and limb ataxia, pyramidal tract signs, and a prominent axonal sensory polyneuropathy. Bulbar signs are infrequent and eye movements are preserved. The median age of onset is 39 years. SCA4 has been linked to chromosome 16q22.1, but the mutation remains unknown (Subramony and Nance, 1998).

Spinocerebellar ataxia type 5. SCA5 presents with a more pure cerebellar syndrome with a comparatively benign clinical course that does not shorten life span. The typical age of onset is in the third or fourth decades, although a range of 10 to 68 years has been described. Anticipation is evident. SCA5 maps to chromosome 11, but the mutation responsible for the disease remains unknown. SCA5 has been found in a family descended from the grandparents of President Abraham Lincoln (Ranum et al, 1994).

Spinocerebellar ataxia type 6. SCA6 presents typically with a pure cerebellar syndrome showing progressive gait and limb ataxia with dysarthria. Other features less commonly seen include nystagmus, slow saccades,

KEY POINTS:

- The age of onset and severity of SCA1 correlates with the length of the CAG expansion, where the longer expansion produces an earlier onset and more severe disease presentation. Anticipation is evident in successive generations, resulting from amplification of the CAG repeat during transmission from parent to offspring.
- Several cases have been described in which the SCA2 genotype presented as a seemingly typical case of familial dopa-responsive parkinsonism.
- Type 4 SCA3/MJD has a predominantly parkinsonian presentation that may be dopa responsive.

KEY POINTS:

- The SCA6 gene sequence has the greatest intergenerational stability of all the spinocerebellar ataxias. Point mutations in this same gene have been reported to cause episodic ataxia type 2 or familial hemiplegic migraine.
- Extreme anticipation in age of onset may cause the onset of disease in a child to precede the onset of disease in a parent, thus possibly mimicking a sporadic onset of disease.

pyramidal tract signs, proprioceptive sensory loss, ophthalmoplegia (primarily impaired upgaze), dystonia, and parkinsonism. Positional vertigo and episodic ataxia have been described (Jen et al, 1998). The typical age of onset is later than in the other SCAs, with a mean of 50 years and a range of 30 to 70 years of age (**Case 9-3**). SCA6 is caused by an expanded CAG repeat in the alpha 1A voltage-gated calcium-channel subunit gene on chromosome 19p13. Normal alleles have 4 to 20 repeats, while expanded alleles have 21 to 33 repeats. This gene sequence has the greatest intergenerational stability of all the SCAs. Point mutations in this same gene have been reported to cause episodic ataxia type 2 or familial hemiplegic mi-

graine (Evidente et al, 2000; Paulson and Ammache, 2001; Subramony and Nance, 1998).

Spinocerebellar ataxia type 7.

SCA7 presents with progressive ataxia and visual loss due to a maculopathy, optic atrophy, and pigmented retinopathy. Childhood-onset cases are more rapidly progressive and manifest upper motor neuron signs, seizures, myoclonus, and dementia. Adult-onset cases may also present with pyramidal tract signs, bulbar signs, slow saccades, supranuclear ophthalmoplegia, and extrapyramidal signs (rare) in the later stages of the disease. The age of onset may range from 2 to 65 years. Extreme anticipation in age of onset may cause the onset of disease in a child to precede the onset of disease in a parent,

Case 9-1

A 60-year-old man presented with a 4- to 5-year history of progressive gait instability. He noted some impairment in coordination of the upper extremities and occasional dysphagia with solids. He denied any sensory symptoms, tremor, weakness, or any other involuntary movements. His father developed gait ataxia in his late 60s. The patient has a sister who walks with a cane and a brother who is wheelchair bound due to poor balance. He has three children, the eldest showing some gait instability, and the younger two appearing neurologically normal.

On examination, he showed normal vital signs and mental status. Cranial nerve examination revealed slow saccades and slight perioral myoclonus. The motor examination was notable only for mild bilateral lower extremity spasticity, with muscle strength and bulk intact. Finger-to-nose and heel-to-shin were ataxic in the left extremities, and rapid alternating movements were slow and irregular bilaterally. Sensory testing revealed diminished vibration in the distal lower extremities. Deep tendon reflexes were absent in the lower extremities. The right plantar response was extensor; the left was flexor. His gait was wide based, spastic, and ataxic. He was unable to tandem walk.

Magnetic resonance imaging of the brain showed cerebellar atrophy. Based on the positive family history, genetic testing for ataxia was pursued and revealed an expanded CAG repeat length of 72 on the SCA3 locus, confirming a diagnosis of SCA3, also known as Machado Joseph's disease (MJD).

Comment. This case demonstrates one of the many phenotypic variations of SCA3. The initial symptoms typically involve gait ataxia of insidious onset and slow progression. Three successive generations have been affected, which confirms the autosomal dominant mode of inheritance and provides a strong rationale for pursuing genetic testing for diagnostic confirmation.

Case 9-2

The 40-year-old daughter of the patient in **Case 9-1** presented with a 3-year history of a decline in her balance where she staggers occasionally when walking. She has developed tightness in the legs and some difficulty in her ability to run. She denied any sensory symptoms, weakness, or bowel or bladder incontinence.

Her mental status and cranial nerve examinations were normal. Bilateral lower extremity spasticity was noted without any muscle weakness. The patellar response was hyperreflexic, and ankle clonus was present bilaterally. The plantar response was extensor bilaterally. Coordination testing was normal except for slight ataxia in the heel-to-shin maneuver on the left. Gait was spastic and ataxic. Sensory examination was normal.

Magnetic resonance imaging revealed severe cervical spondylosis at C6-7 with spinal cord compression.

Comment. This case demonstrates a combination of ataxia with pyramidal tract signs that can be seen in SCA3. Age of onset for this patient was approximately 18 years earlier than the affected father, indicating possible anticipation characteristic of CAG-repeat diseases. The pyramidal signs appeared a bit out of proportion to the ataxia, thus prompting imaging that uncovered a possible reversible cause for this patient's symptoms. This case illustrates the importance of considering alternative diagnostic possibilities for neurologic signs and symptoms in patients with a positive family history for SCA.

thus possibly mimicking a sporadic onset of disease. The SCA7 mutation is an expanded CAG repeat in the ataxin-7 gene on chromosome 3p12. Normal alleles contain 4 to 35 repeats, and expanded alleles contain 37 to 200 CAG repeats. The normal function of ataxin-7 is unknown (Evidente et al, 2000; Paulson and Ammache, 2001; Subramony and Nance, 1998).

Spinocerebellar ataxia type 8. SCA8 presents with adult-onset gait and limb ataxia with eventual bulbar signs, eye movement abnormalities, limb spasticity, and vibratory sensory loss. Speech may be disproportionately affected at an early stage relative to the cerebellar signs. An age of onset ranging from 13 to 65 years has been reported in one family. The SCA8 mutation is an expanded CTG repeat on chromosome 13q21, which is located in an untranslated region of the chromosome. The expanded allele has been reported as 107 to 127 CTG repeats in length, whereas the normal

allele is 7 to 20 repeats in length. Unlike the other SCAs where anticipation is greater along a paternal lineage of transmission, SCA8 has a maternal bias (Day et al, 2000).

Spinocerebellar ataxia type 9. SCA9 is unassigned.

Spinocerebellar ataxia type 10. SCA10 presents with an almost pure cerebellar syndrome with some affected individuals also manifesting seizures. This SCA has been described thus far only in families of Mexican descent, implying a founder effect, meaning a new mutation in an isolated population. The typical age of onset is in the third or fourth decade, although the disease can start in childhood. The SCA10 mutation is an expanded ATTCT repeat in an untranslated region of chromosome 22q13. Normal alleles are 10 to 22 pentanucleotides in length, whereas mutated alleles have been reported as long as 800 to 4500 repeats in length. Anticipation has been described

(Matsuura et al, 2002; Paulson and Ammache, 2001).

Spinocerebellar ataxia type 11. SCA11 presents with mainly cerebellar signs and hyperreflexia and overall has a milder disease course compatible with a normal life expectancy. The mean age of onset reported in two British families is 25 years. SCA11 has been mapped to chromosome 15q14, but the exact mutation type is not yet known (Worth et al, 1999).

Spinocerebellar ataxia type 12. SCA12 has been described in two families thus far, presenting with head and upper extremity action tremor, ataxia, bradykinesia, and hyperreflexia. Dementia may occur in individuals with a later age of onset or in those subjects at later stages of the disease. Psychiatric disorders such as anxiety and depression may also be observed. The age of onset ranges from 8 to 55 years. The SCA12 mutation is an expanded CAG repeat in an untranslated region

of the PPP2R2B gene on chromosome 5p31-p33, which codes for a subunit of the enzyme protein phosphatase 2A. The normal allele is 9 to 28 repeats in length, and the expanded allele can be 55 to 78 repeats in length (Holmes et al, 2001).

Spinocerebellar ataxia type 13. SCA13 has been reported only among French families and presents in early childhood with limb ataxia, dysarthria, nystagmus, psychomotor developmental delays, and mental retardation. SCA13 has been linked to chromosome 19 (Paulson and Ammache, 2001).

Spinocerebellar ataxia type 14. SCA14 has been described in a single Japanese family, with affected individuals manifesting ataxia, axial myoclonus, and tremor. Age of onset has been reported between 12 and 42 years. SCA14 maps to chromosome 19q (Paulson and Ammache, 2001).

Spinocerebellar ataxia type 15. SCA15 is tentatively assigned to a single

Case 9-3

A 63-year-old woman presented with a 10-year history of episodic vertigo and dysequilibrium for which she was diagnosed with "Ménière's disease." Over the past 3 years she developed progressive worsening of balance and, more recently, diplopia. Her family history is remarkable for a father with "Ménière's disease."

Vital signs and mental status were normal. Cranial nerve testing revealed slow vertical and horizontal saccades, a skew deviation with lateral gaze, and slight dysarthria. Coordination testing revealed dysrhythmic rapid alternating movements in the left upper extremity and ataxic heel-to-shin bilaterally. The gait was wide based and ataxic. The motor, sensory, and deep tendon reflex examinations were normal.

Magnetic resonance imaging of the brain showed isolated mild cerebellar atrophy. Genetic testing was positive for an expanded CAG repeat length of 24 on chromosome 19, confirming the diagnosis of SCA6. Diamox was given, which provided approximately 25% improvement in the unsteadiness and episodic vertigo.

Comment. This case illustrates typical features of SCA6 that can include initial episodic vertigo and ataxia followed by progressive gait ataxia and possible ophthalmoplegia. The age of onset is typically older than the other SCAs; thus a seemingly negative family history is possible. With a negative family history, the yield of genetic testing is overall low (ie, 4% to 5%). In this case, however, the SCA6 mutation was confirmed, providing a definitive diagnosis and eliminating the need to pursue additional diagnostic testing.

kindred involving eight affected individuals who presented with a pure cerebellar ataxic syndrome. The age of onset varied from mid-childhood to middle age. Magnetic resonance imaging revealed pure vermis atrophy. The gene mutation or chromosome linkage has not yet been identified (Storey et al, 2001).

Spinocerebellar ataxia type 16. SCA16 has been described in a four-generation Japanese family whose most affected individuals manifested a pure cerebellar syndrome with gait and limb ataxia, dysarthria, and nystagmus. A few subjects also had a head tremor. The age of onset ranged from 20 to 66 years. Anticipation was not seen in this family. SCA16 maps to chromosome 8q22 (Miyoshi et al, 2001).

Spinocerebellar ataxia type 17. SCA17 has been described in four Japanese pedigrees with affected individuals manifesting initially with gait ataxia and later development of dementia, bradykinesia, dysmetria, dysdiadochokinesis, and hyperreflexia. Abnormalities in eye movements were not present. The mean age of onset was in the third decade. The SCA17 mutation is an expanded CAG/CAA repeat in the TATA-binding protein gene. The normal allele length is 29 to 42 repeats, whereas the expanded allele contains 47 to 55 repeats (Nakamura, 2001).

Spinocerebellar ataxia type 19. SCA19 has been described in a single Dutch kindred, with affected individuals presenting with a mild ataxic syndrome accompanied in some by myoclonus, cognitive impairment, and an irregular, slow-frequency, postural tremor. Pyramidal tract signs and peripheral neuropathy were sometimes seen. SCA19 links to chromosome 1p21-q21. A second form of familial hemiplegic migraine maps to this locus, implying that a pathologic change in an ion channel may be the result of the responsible mutation (Verbeek et al,

2002). The age of onset for this disease ranges from 20 to 45 years (Bird, 2004).

Spinocerebellar ataxia type 21. SCA21 has been described in a French family, whose affected members manifested a slowly progressive gait and limb ataxia. Akinesia, rigidity, tremor, hyporeflexia, and mild cognitive impairment were variably expressed. SCA21 maps to chromosome 7p21.3-p15.1 (Vuillaume et al, 2002). The mean age of onset of disease is 17 years with a range of 6 to 30 years (Bird, 2004).

Dentatorubral-pallidolusian atrophy. Dentatorubral-pallidolusian atrophy (DRPLA) presents with progressive ataxia, chorea myoclonus, epilepsy, dystonia, dementia, and parkinsonism. Patients with adult-onset DRPLA may appear phenotypically similar to patients with Huntington's disease. DRPLA is rare, reported mostly in individuals of Japanese descent, with the exception of an African American kindred in North Carolina with DRPLA that was termed the Haw River syndrome. The age of onset is variable, ranging from childhood to late adulthood. Anticipation has been observed, and age of onset (inversely) and disease severity correlate with repeat length. The DRPLA mutation is an expanded CAG repeat in the atrophin-1 gene of chromosome 12p12. Normal alleles have 7 to 34 repeats, whereas the abnormal alleles have 54 to 75 repeats (Evidente et al, 2000).

Episodic Ataxias

Episodic ataxia type 1. Episodic ataxia type 1 (EA-1) is a familial episodic ataxia with interictal myokymia. Affected individuals manifest attacks of ataxia and dysarthria lasting only seconds to minutes. The myokymia appears in the periorbital or perioral muscles and in the fingers. Attacks are precipitated by exercise and startle. Age of onset is during late childhood or early adolescence. Ataxic attacks

KEY POINT:

- Patients with adult-onset dentatorubral-pallidolusian atrophy may appear phenotypically similar to patients with Huntington's disease.

KEY POINTS:

- Episodic ataxia type 2 is caused by a point mutation in the calcium channel gene CACNL1A4 on chromosome 19, which is the same gene sequence involved in SCA6 and familial hemiplegic migraine.
- Individuals with an older age of onset of Friedrich ataxia appear to have a milder, more slowly progressive form of the disease; skeletal abnormalities, cardiomyopathy, and areflexia may not be present.
- Ataxia with isolated vitamin E deficiency clinically resembles the Friedrich ataxia phenotype.

may be decreased with acetazolamide, and myokymia may be aborted with phenytoin. EA-1 is caused by a missense mutation in the voltage-gated potassium channel on chromosome 12p13 (Evidente et al, 2000).

Episodic ataxia type 2. Episodic ataxia type 2 (EA-2) is a familial episodic ataxia with interictal nystagmus. Affected individuals present with attacks of ataxia, dysarthria, nausea, vertigo, diplopia, and oscillopsia lasting minutes to days, and many subjects also have migraine headaches. Attacks may be precipitated by emotional stress and exercise. Age of onset of disease is usually in childhood or adolescence. The severity and frequency of attacks may be decreased with acetazolamide. EA-2 is caused by a point mutation in the calcium channel gene CACNL1A4 on chromosome 19, which is the same gene sequence involved in SCA6 and familial hemiplegic migraine (Denier et al, 2001).

Autosomal Recessive Inherited Ataxias

Friedreich ataxia. Friedreich ataxia (FA) presents with gait and limb ataxia, dysarthria, absent deep tendon reflexes in the lower extremities, and proprioceptive sensory loss. Sensorineural hearing loss and optic atrophy can be seen. Severe kyphoscoliosis and a cardiomyopathy are other typical non-neurologic features of FA. The age of onset is typically before age 25, although the reported range is broad, from 4 to 60 years. Individuals with an older age of onset appear to have a milder more slowly progressive form of the disease; skeletal abnormalities, cardiomyopathy, and areflexia may not be present. The FA mutation involves an unstable GAA trinucleotide repeat expansion for the frataxin gene on chromosome 9q13. Normal alleles contain 6 to 36 GAA repeats, whereas mutated ex-

panded alleles contain 90 to 1300 repeats. The larger trinucleotide expansion is associated with an earlier age of onset and a more malignant form of the disease (Di Donato et al, 2001). Compound heterozygotes have also been identified, with a trinucleotide repeat expansion in one allele, and either a non-sense mutation, missense point mutation, or initiation codon mutation in the other allele (Kaplan, 2002). Unlike the SCAs, where a toxic gain of function occurs with the translation of an expanded CAG repeat, in FA, the function of frataxin is presumed lost as a result of the genetic mutation.

Ataxia-telangiectasia. Ataxia telangiectasia presents with progressive ataxia, oculocutaneous telangiectasia, oculomotor apraxia, choreoathetosis, dystonia, dysarthria, myoclonus, sensory loss, hyporeflexia, and cognitive decline. Other non-neurologic signs include a high incidence of malignancies (leukemias and lymphomas are especially common) and impaired cellular and humoral immunity, with frequent pulmonary infections occurring as a result. Serum immunoglobulin A is either extremely low or absent, and serum immunoglobulin E and immunoglobulin M are also reduced. Serum carcinoembryonic antigen and serum α -fetoprotein are typically elevated. Ataxia telangiectasia begins in infancy, and the mean age at death is 20. Ataxia telangiectasia is caused by a mutation in the ATM gene on chromosome 11q22-23, which codes for a large protein that is involved in the repair of damaged DNA. The exact mechanism by which this mutation produces ataxia is not known (Di Donato et al, 2001).

Ataxia with isolated vitamin E deficiency. Ataxia with isolated vitamin E deficiency clinically resembles the FA phenotype. Affected individuals present with progressive ataxia, an axonal sensory neuropathy, head tremors, and pigmentary changes of the

retina. Some individuals also manifest skeletal deformities and a cardiomyopathy. Age of onset is usually less than 20 years, with a range of 2 to 52 years reported. The responsible mutation is in the gene on chromosome 8 encoding for the α -tocopherol transfer protein. Vitamin E supplementation can halt the progression of the disease and may improve some existing deficits (Di Donato et al, 2001).

Abetalipoproteinemia. Abetalipoproteinemia presents with ataxia, a malabsorption syndrome that may be mild or transient, and a retinopathy. Laboratory findings can include acanthocytes on a peripheral blood smear, low serum total cholesterol, absent or low apolipoprotein B-containing proteins, low vitamin A, E, and K levels, and abnormal serum protein electrophoresis. Mutations have been described in the microsomal triglyceride transfer protein (Di Donato et al, 2001).

Early-onset cerebellar ataxia with retained reflexes. Early-onset cerebellar ataxia with retained reflexes presents with progressive ataxia, dysarthria, spasticity, impaired ocular saccades, and retained deep tendon reflexes, unlike FA. Cardiac and skeletal abnormalities are not seen. The mean age of onset is around 9 years. The responsible genetic mutation has not been identified. However, genetic heterogeneity for this disorder is suspected (Paulson and Ammache, 2001).

Progressive myoclonic ataxia and progressive myoclonic epilepsy. Progressive myoclonic ataxia (PMA) and progressive myoclonic epilepsy (PME) are childhood-onset disorders that are also known as Ramsay Hunt syndrome and Unverricht-Lundborg disease, respectively. PMA presents with progressive ataxia and action myoclonus. The PMA phenotype may also be caused by mitochondrial disorders (eg, myoclonic epilepsy with ragged red fiber disease; Kearns-Sayre syndrome;

neuropathy, ataxia, retinitis pigmentosa syndrome); celiac disease; and DRPLA). PME may have similar findings to PMA but also manifests with seizures and cognitive decline. The PME phenotype may also be caused by ceroid lipofuscinosis, Lafora's disease, and the sialidoses. In Unverricht's disease, mutations in the cystatin B gene on chromosome 21q22, which codes for a cysteine protease inhibitor, have been identified (Evidente et al, 2000; Paulson and Ammache, 2001).

Xeroderma pigmentosum and Cockayne syndrome. Xeroderma pigmentosum and Cockayne syndrome, along with ataxia telangiectasia, share a defect in DNA repair as the responsible mechanism of disease. Xeroderma pigmentosum presents with progressive ataxia, cognitive regression, choreoathetosis, deafness, extreme photosensitivity, and skin cancers. Cockayne syndrome presents with many of the same features but also microcephaly, progeria, basal ganglia calcification, and pigmentary retinal degeneration. Age of onset is in early childhood or adolescence (Paulson and Ammache, 2001).

Marinesco-Sjögren syndrome. Marinesco-Sjögren syndrome is a rare disorder presenting with cerebellar ataxia, cataracts, hypotonia, mental retardation, myopathy, and hypogonadism. Age of onset is in infancy or early childhood. The responsible genetic mutation is not known, but the suspected disease mechanism may be a disorder of lysosomal storage.

Ataxia with hypogonadism. Ataxia with hypogonadism has been called Holmes ataxia and presents with a phenotype as the name implies. The age of onset is between the fourth and sixth decades. The genetic mutation or biochemical mechanism of disease is unknown (Evidente et al, 2000).

Infantile-onset spinocerebellar ataxia. Infantile-onset spinocerebellar ataxia has been described only in the

KEY POINT:

- Vitamin E supplementation can halt the progression of ataxia with isolated vitamin E deficiency and may improve some existing deficits.

Finnish population and presents with ataxia, sensory neuropathy, hyporeflexia, hypotonia, athetosis, ophthalmoplegia, and deafness. Hypogonadism may be seen in affected females. A candidate gene has been identified on chromosome 10q24 (Evidente et al, 2000).

Refsum's disease. Refsum's disease, a rare disorder, presents with cerebellar ataxia, retinitis pigmentosa, chronic polyneuropathy, and an elevated cerebrospinal fluid (CSF) protein. Mutation of the phytanoyl-CoA hydroxylase gene leads to a deficiency of the translated peroxisomal enzyme, resulting in abnormal accumulation of phytanic acid. Dietary restriction of phytanic acid may prevent progression of disease when caught in the early stages (Di Donato et al, 2001).

Wilson's disease. Wilson's disease has a variable phenotypic expression, manifesting (either in isolation or combination) as a hepatic disease, extrapyramidal disorder, and/or psychiatric syndrome. The "pseudosclerotic" phenotype presents mainly with ataxia, with magnetic resonance imaging findings often mimicking demyelinating disease. The responsible genetic mutation lies in the ATP7B gene on chromosome 13 that codes for a copper-binding adenosine triphosphatase. This mutation results in abnormal excessive storage of copper in the liver and basal ganglia, leading to the clinical syndromes noted above.

X-linked spinocerebellar ataxias. X-linked spinocerebellar ataxias have also been described but will not be covered in the context of this review.

Sporadic Ataxias

The differential diagnosis for sporadically occurring ataxia is broad and includes the following causes for acute and chronic cerebellar diseases in addition to noninherited cerebellar degeneration: multiple sclerosis, tumor (primary central nervous system

[CNS] or metastatic), stroke, cerebellar malformations (eg, Arnold-Chiari, Dandy-Walker), cervical spondylosis, paraneoplastic syndromes, alcohol toxicity, acquired vitamin E deficiency, toxins (mercury, lead, thallium, carbon disulfide), multisystem atrophy/olivopontocerebellar atrophy, metabolic disorders (hyperammonemia and hypothyroidism), psychogenic disorders, mitochondrial disorders, infectious or postinfectious diseases (rhombencephalitis, Creutzfeldt-Jakob disease), leukodystrophies, storage diseases (ceroid lipofuscinosis, GM2-gangliosidosis, Niemann-Pick type C), metachromatic leukodystrophy, autoimmune disorders (gluten hypersensitivity with antibodies to glutamic acid decarboxylase or antigliadin antibodies associated with celiac disease, neuro-Behçet's disease, the Miller-Fischer variant of Guillain-Barré syndrome), anticonvulsant medication (acute phenytoin toxicity and chronic cerebellar degeneration, carbamazepine toxicity, and clonazepam toxicity), and coenzyme Q10 deficiency (Fonte et al, 2003; Gilman 1997; Lamperti et al, 2003; Paulson and Ammache, 2001).

Pathogenesis of Inherited Ataxias

Molecular pathology. The exact mechanisms through which the known genetic mutations produce the spinocerebellar ataxia syndromes are not entirely understood. However, one could categorize them, in part, into the resultant effects of translated CAG repeats, untranslated trinucleotide repeats, point mutations in ion channel genes, and defects in DNA repair (Klockgether et al, 2000). Deciphering the exact pathophysiologic mechanism of disease is important for developing specific therapies that may offer symptomatic benefit or modify the expression and progression of the disease.

In SCA1, the expanded CAG repeat gene codes for a polyglutamine peptide within the protein ataxin-1. The normal function of ataxin-1 is not entirely understood. This expanded polyglutamine tail is thought to cause a toxic gain of function of the ataxin-1 protein through abnormal protein conformation or abnormal interaction with other nuclear proteins. More specifically, mutant ataxin-1 has been shown to cause a redistribution of the nuclear matrix-associated promyelocytic leukemia protein, which results in disruption of the nuclear matrix (Klockgether et al, 2000). The abnormal ataxin-1 protein forms neuronal intranuclear inclusions, which may either be responsible for the toxicity of this mutant protein or may be a protective mechanism to sequester this aberrant protein. Ataxin-1 is expressed ubiquitously in nervous and non-nervous tissue and may preferentially affect the cerebellum through its colocalization with leucine-rich acidic nucleoprotein, which is a protein unique to Purkinje cells (Klockgether et al, 2000).

The function of the ataxin-3 protein is unknown, but it is localized in the cell cytoplasm and expressed ubiquitously throughout the body. In SCA3, mutant ataxin-3 accumulates abnormally in the cell nucleus of vulnerable neurons, forming insoluble inclusions, much like ataxin-1 (Klockgether et al, 2000).

In SCA7, mutant ataxin-7 localizes in neuronal intranuclear inclusions. The normal function of ataxin-7 is unknown. Ataxin-7 is expressed ubiquitously in CNS and peripheral tissues. Ataxin-7b is an alternatively spliced transcript found only in the CNS, which may be why nervous tissue is selectively affected in this disease (Einum et al, 2003). It is possible that mitochondrial malfunction may be responsible for the SCA7 disease. Muscle biopsies have shown scant ragged red

fibers and subsarcolemmal accumulations of rounded abnormal mitochondria; reduced activity of complex I and IV of the respiratory chain has been reported (Evidente et al, 2000). The exact mechanism linking the genetic mutation to mitochondrial dysfunction is not known.

In SCA17, the mutation is an expanded CAG/CAA repeat in the TATA-binding protein gene, which codes for a general transcription initiation factor protein. Postmortem studies showed neuronal intranuclear inclusion bodies similar to SCA1 and SCA3, but these stain positive for antibodies against ubiquitin, polyglutamine peptides, and TATA-binding proteins (Nakamura, 2001).

In DRPLA, again, intranuclear protein aggregation is seen in postmortem brain tissue samples. The DRPLA protein binds to glyceraldehyde-3-phosphate dehydrogenase, implying that this protein may have gained the toxic function of reducing cellular energy production, thus increasing a neuron's susceptibility to degeneration (Evidente et al, 2000).

In SCA8, the mutation is an expanded CTG repeat located in an untranslated region of the chromosome. Klockgether and colleagues speculate that this expansion may lead to a toxic gain of function at the RNA rather than protein level (Klockgether et al, 2000).

In SCA12, the expanded CAG repeat lies in the putative promoter region for the PPP2R2B gene, which encodes a CNS-specific subunit for the protein phosphatase PP2A. This promoter mutation leads to abnormal expression of the adjacent gene. The specificity of the PPP2R2B subunit protein for the CNS explains why disease manifestation is restricted to the CNS while the protein phosphatase is ubiquitously expressed in all cell types. Unlike many of the ataxin proteins, the function of PP2A is known: PP2A is a phosphatase regulating many cellular processes

KEY POINTS:

- In SCA1, the expanded CAG repeat gene codes for a polyglutamine peptide within the protein ataxin-1 are thought to cause a toxic gain of function of the ataxin-1 protein through abnormal protein conformation or abnormal interaction with other nuclear proteins.
- In SCA8, expansion of a CTG repeat located in an untranslated region of the chromosome may lead to a toxic gain of function at the RNA rather than protein level.

KEY POINT:

- In episodic ataxia type 1 and episodic ataxia type 2, a point mutation results in dysfunction of a potassium or calcium channel protein.

including cell growth and differentiation, DNA replication, regulation of kinase cascades, ion channel function, microtubule assembly, neurotransmitter release, and apoptosis (Holmes et al, 2001).

In FA, the abnormal protein product is frataxin, which is an iron-binding mitochondrial protein that may control iron homeostasis. Based on what is known about frataxin, theories on the pathophysiology of FA include abnormal iron accumulation in the mitochondria of affected tissue, decreased cellular adenosine triphosphate production, increased production of toxic reactive oxygen species, impaired mitochondrial DNA repair, and altered cellular phospholipid metabolism. Magnetic resonance imaging reveals increased iron deposition in the dentate nucleus, and autopsy and biopsy studies have shown iron deposits in myocardial cells, thus linking the putative pathophysiologic mechanisms to the organ or tissue types involved in the disease (Kaplan, 2002).

In EA-1 and EA-2, a point mutation results in dysfunction of a potassium or calcium channel protein. In EA-2, the calcium channel protein CACNL1A4 is preferentially expressed in Purkinje cells, thus explaining selective pathologic and clinical manifestations involving the cerebellum (Klockgether et al, 2000).

Ataxia telangiectasia is caused by a mutation in the ATM gene on chromosome 11q22-23 that codes for a large protein that is involved in the repair of damaged DNA. How this mutation produces ataxia is not known.

Gross and microscopic pathology. Studies of the gross and microscopic neuropathology of the brain, spinal cord, and peripheral nerves have revealed significant heterogeneity equaling the diversity of the clinical phenotypes noted among the inherited ataxias. Koeppen summarized some of the main pathologic features of the

various hereditary ataxia subtypes. For FA, the spinal cord is more severely involved than the cerebellum, with thoracic cord and dorsal nerve root atrophy noted on gross examination. Degeneration of the lateral corticospinal tracts, dorsal columns, dorsal spinocerebellar tracts, and dorsal nuclei of Clarke are seen on microscopic analysis. Neuronal loss is found in the dentate nucleus of the cerebellum, but the cerebellar cortex is spared (Koeppen, 1998). SCA3/MJD similarly shows sparing of the cerebellar cortex, but neuronal loss and/or degeneration can be found in the dentate nucleus, substantia nigra, subthalamic nucleus, red nucleus, globus pallidus, brain stem motor nuclei, dorsal nucleus of Clarke, and anterior horns (Sequeiros and Coutinho, 1993). In pure cerebellar atrophy subtypes such as SCA6, cerebellar cortical atrophy is found with secondary degeneration of the inferior olives, but the dentate nucleus and other CNS structures are spared. For other SCA subtypes with mixed cerebellar, bulbar, pyramidal, and extrapyramidal features, the pathologic findings typically correlate with the clinical features and systems involved and often vary with the severity or duration of the disease process. A varying combination of atrophy or degeneration of the following structures can be found: cerebellar cortex, inferior olive, dentate nucleus, basis pontis, pontine tegmentum, middle cerebellar peduncles, posterior columns, and, in SCA2, cerebral cortex. Magnetic resonance imaging, likewise, shows varying combinations of cerebellar cortex, cerebral cortex, cerebellar peduncle, brain stem, and spinal cord atrophy. The presence of oligodendroglial cytoplasmic inclusions on microscopic examination indicates a nonhereditary form of multisystem atrophy, although such inclusions may be found on occasion in SCA1 (Koeppen, 1998).

Neurochemistry. Investigations have failed to identify a particular neurotransmitter imbalance or deficiency, akin to the dopamine deficiency in Parkinson's disease, that may explain the underlying pathophysiologic mechanism of disease manifestation in ataxias. Serotonin may play a major role in normal cerebellar function. The dorsal raphe nucleus projects to the 5-hydroxytryptamine-1 receptors, which are located in the molecular, granule, and Purkinje cell layers. Deep cerebellar nuclei contain serotonergic cell bodies. Postmortem and CSF studies in ataxias of various causes have implicated a role for catecholamines in cerebellar dysfunction where noradrenaline levels have been reduced in the cerebellar cortex, CSF homovanillic acid (dopamine metabolite) levels have been reduced, and striatonigral dopamine nerve terminal loss has been shown. Cholinergic mechanisms have been implicated as well, where acetylcholine is the neurotransmitter in mossy fiber projections, and postmortem studies in ataxia patients of varying causes have shown reduced muscarinic receptor density in the cerebellar molecular and granule cell layers and reduced choline acetyltransferase and acetylcholinesterase in the cerebellar cortex. Finally, γ -aminobutyric acid (GABA) is a neurotransmitter for Purkinje, stellate, Golgi, and basket cells in the cerebellum. Postmortem studies, again in patients with ataxia of varying causes, have shown reduced GABA levels in the cerebellum, reduced GABA receptor density in the granule cell layer, increased benzodiazepine receptor density in the dentate nucleus, and reduced GABA levels in the CSF (Oertel, 1993).

EPIDEMIOLOGY

The overall prevalence of the autosomal dominant inherited ataxias is

about 1 to 5 in 100,000. This prevalence can vary geographically due to presumed founder effects, where, for example, SCA3/MJD occurs at a rate of 1 in 4000 in the Azores. It is estimated that approximately 20% to 40% of inherited ataxias have yet to be genotypically defined. In the United States, among the autosomal dominant inherited ataxias, SCA3/MJD is the most common form, with a frequency of 20.8%, followed by SCA2 and SCA6 at 15.2% each, SCA1 at 5.6%, and SCA7 at 4.5% (Moseley et al, 1998). FA is the most common autosomal recessive inherited ataxia, occurring with a prevalence of about 1 in 50,000 (Kaplan, 2002). Cerebellar degeneration cases that seem sporadic with a negative family history may demonstrate positive autosomal dominant genetic testing about 4% of the time and positive testing for FA about 5.2% of the time (Moseley et al, 1998). Ataxia telangiectasia is the second most common among the recessive ataxias, with a prevalence of about 1 in 100,000 live births (Di Donato et al, 2001).

Diagnostic Evaluation

When the ataxia is known to be inherited as either an autosomal dominant or recessive condition, genetic testing can be useful to confirm the diagnosis of the disease. In the absence of a positive family history, the yield of the genetic testing is only about 4% to 5%. New mutations are possible, but anticipation, when the offspring becomes symptomatic before the parent, nonpaternity, and early death of a presymptomatic parent are all scenarios where the family history can be misleading. Genetic counseling, either by the neurologist or a geneticist, is an important component to the testing process in symptomatic/confirmatory cases to ensure the individual patient understands the implications

KEY POINTS:

- The overall prevalence of the autosomal dominant inherited ataxias is about 1 to 5 in 100,000.
- In the United States, SCA3/Machado-Joseph's disease is the most common form of the autosomal dominant inherited ataxias.
- Cerebellar degeneration cases that seem sporadic with a negative family history may demonstrate positive autosomal dominant genetic testing about 4% of the time and positive testing for Friedreich's ataxia about 5.2% of the time.

KEY POINTS:

- The following genetic tests for ataxia are commercially available at this time: Friedreich's ataxia, SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA17, and DRPLA.
- For the inherited ataxias, presymptomatic genetic testing carries the same ethical and psychological concerns as are expressed for Huntington's disease. This testing should therefore follow the same guidelines published for the presymptomatic genetic testing of Huntington's disease.

of a positive test result. The following genetic tests for ataxia are commercially available at this time: FA, SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA17, and DRPLA.

Evaluation of noninherited ataxias addresses the possible causes of sporadic or secondary ataxias as discussed above and could include any combination of the studies summarized in **Table 9-2** (Gilman, 1997).

Presymptomatic Genetic Testing

For the inherited ataxias, presymptomatic genetic testing carries the same ethical and psychological concerns as are expressed for Huntington's disease; this testing should therefore follow the same guidelines published for the presymptomatic genetic testing of Huntington's disease. Careful neurologic evaluation, psychological evaluation and counseling, and genetic counseling are recommended (Goizet et al, 2002; International Huntington Association and World Federation of Neurology, 1994).

Treatment Options

Ataxias known to be secondary to a separate disease process may improve by treating the specific underlying disease. For example, ataxia due to vitamin E deficiency can improve with supplementation, and paraneoplastic cerebellar disorders can improve when the underlying malignancy is successfully treated or cured.

Symptomatic or disease-modifying treatment options for inherited or sporadic degenerative ataxias are limited. EA-1, EA-2, and SCA6 (in the early stages) may respond to acetazolamide. Parkinsonian features in SCA2 or SCA3/MJD may respond to levodopa (Lu et al, 2002). Antioxidant therapy may have a role in treating some of the ataxias. For example, idebenone

TABLE 9-2 Diagnostic Studies in the Evaluation of Ataxia

- ▶ Magnetic resonance imaging (brain and C-spine)
- ▶ Lumbar puncture
- ▶ Thyroid function studies
- ▶ Heavy metal screen
- ▶ Vitamin E levels
- ▶ Ataxia paraneoplastic antibody panel
- ▶ Serum cholesterol and plasma lipoprotein profile
- ▶ Serum ceruloplasmin
- ▶ 24-Hour urine copper
- ▶ Mitochondrial DNA mutations
- ▶ Serum lactate and pyruvate
- ▶ Muscle biopsy
- ▶ Serum iron
- ▶ Blood smear for acanthocytes
- ▶ Antigliutamic acid decarboxylase antibodies
- ▶ Antigliadin antibodies
- ▶ Very long chain fatty acids
- ▶ Hexosaminidase A or B
- ▶ Serum protein electrophoresis
- ▶ Anticonvulsant drug levels
- ▶ Skin or rectal biopsy
- ▶ Bone marrow biopsy

Adapted from Gilman S. Clinical features and treatment of cerebellar disorders. In: Watts RL, Koller WC, eds. Movement disorders: neurologic principles and practice. New York: The McGraw-Hill Companies, 1997:577–585. Reprinted with permission from The McGraw-Hill Companies.

is a free radical scavenger that was shown in one small controlled study to possibly improve the cardiomyopathy in FA (Mariotti et al, 2003) and in another small series to improve ataxia rating scale scores in FA (Artuch et al,

2002). *N*-acetylcysteine, a precursor to the antioxidant glutathione, reduced seizure frequency and myoclonus in Unverricht-Lundborg disease where an excess in the extracellular superoxide dismutase activity, producing increased free radical production, serves as a putative mechanism for the underlying disease process (Edwards et al, 2002; Hurd et al, 1996). *N*-acetylcysteine use in other forms of ataxia has not proven to be beneficial. Finally, one case report described a patient with SCA2 with a severe resting and action tremor that improved with thalamic deep brain stimulation (Pirker et al, 2003).

Most of the other agents tried in either an open-label or double-blind fashion for the treatment of ataxia were of limited or no success and included thyrotropin-releasing hormone, buspirone, fluoxetine, isoniazid, vigabatrin, physostigmine, choline

and lecithin, propranolol, levodopa, bromocriptine, anticholinergic agents, baclofen, and amantadine (Goetz et al, 1984; Koller, 1984; Manyam, 1986; Monte et al, 2003; Trouillas et al, 1997). Such agents were chosen based on their theoretical ability to modulate cerebellar neurotransmitter or receptor activity. Subjects included in these small studies frequently had ataxia from many different causes. Successful treatments may only be found when the underlying pathophysiologic processes causing the various types of ataxia are understood and treatments are tailored to address this specific mechanism in each ataxia subtype. Until then, nonpharmacologic treatments such as physical, occupational, and speech therapy can be offered to improve or maintain patients' functional capacities or at least to help them adapt to the limitations posed by their condition.

KEY POINT:

- Successful treatments may only be found when the underlying pathophysiologic processes causing the various types of ataxia are understood and treatments are tailored to address this specific mechanism in each ataxia subtype.

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