

Ataxia with Identified Genetic and Biochemical Defects

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Updated: Apr 30, 2009

Background

Hereditary genetic and metabolic disorders involve the nervous system at multiple levels, resulting in varied manifestations; common clinical presentations of such disorders in childhood include the following features in combination:

- Developmental delay
- Neurologic or developmental regression
- Family history of similar symptoms in a sibling or closely related individual
- Episodic alteration in level of consciousness or recurrent neurologic symptoms
- Multisystem involvement (in addition to neurologic systems)
- Development and progression of a particular neurologic sign such as ataxia or seizures

Ataxia is defined as an inability to maintain normal posture and smoothness of movement. Neurologic symptoms and signs such as seizures and movement disorders (eg, dystonia, chorea) may accompany ataxia. Consequently, many variations are encountered in the clinical phenotype, ranging from findings of pure cerebellar dysfunction to mixed patterns of involvement reflecting extrapyramidal pathways, brainstem, and cerebral cortical involvement. A wide range of molecular defects have been identified in which the spinocerebellar pathways are involved.

Despite this remarkable diversity of genetic defects and mechanisms, the pathologic responses within the nervous system are limited in terms of the targeted pathways. This feature likely contributes to significant overlap seen in the clinical presentation. Nevertheless, delineation of the clinical phenotype represents an important first step in the diagnostic process. The clinical phenotype guides the geneticist in a search for appropriate diagnostic tests, reducing costs of laboratory workup.

The group of disorders manifesting with ataxia is expanding constantly (29 spinocerebellar ataxias [SCAs] are now recognized) as the genetic basis for many of the dominant and recessively inherited ataxias are unraveled. Study of subcellular organelle structures has enabled delineation of aspects of mitochondrial, lysosomal, and peroxisomal disorders. However, despite the advances in the understanding of pathogenesis, there has been a lag in the development of effective treatments for this group of disorders.^[1]

As the underlying mechanisms of disease begin to be understood, the inherent challenges are apparent; for instance, several ataxias are caused by defects in DNA repair, while others may result from protein folding and chaperoning defects. Advances in

genomics, proteomics, transcriptomics, and metabolomics are paving the way towards understanding of gene function, protein synthesis and transcription, and gene-gene and protein-protein interactions. These studies hopefully will provide the basis for a new set of designer drugs geared towards individualized treatments.

This article reviews the present understanding of inherited neurologic and metabolic disorders manifesting with ataxia as a clinical feature, focusing on key clinical features, laboratory findings, and pathophysiologic insights gleaned from molecular genetic studies, as well as current treatment strategies in management.^[2]

The cerebellum and its pathways in health and disease

The transverse lobular arrangement of cerebellum has been described extensively in classic neuroanatomical literature. On the other hand, 7 longitudinal mediolateral parallel zones on each side of midline have been described as functional units of the cerebellar cortex. These zones are apparently formed via developmental mechanisms and the cerebellum has expanded mediolaterally with evolution. The medial zone is involved in adaptive control of somatic and autonomic reflexes and compound movements such as locomotion and saccadic eye movements. These functions are common across vertebrate species. The intermediate zone developed in relation to voluntary movement in mammals. The lateral zones are related to higher order functions of the cerebral association area. The most lateral zone in humans is likely to be associated with cognition.

Each zone receives afferents from discrete areas, and the Purkinje cell axons from each area project to a particular region of the cerebellar or vestibular nucleus. The input into the cerebellum is from all 3 peduncles with the ascending input through the inferior and the cortical input through the middle cerebellar peduncle. The superior cerebellar peduncle is responsible predominantly for the output from the cerebellum. The afferents received by the cerebellum have specific functional relevance in terms of occurrence of the pathology and lesion placement. These afferents will be briefly reviewed first. The subsequent sections will focus upon the 5 major functions ascribed to the cerebellum, the putative anatomical pathways, and the structures responsible for these functions and therefore the clinical manifestations of lesions in these structures. These functions are locomotion, postural control, voluntary movements, and finally cognition within the cerebellum.^[3]

Afferents of cerebellum and their functional importance

Most of the afferents enter the cerebellum via mossy or climbing fibers. These 2 fiber systems transmit distinct types of information and influence cerebellar Purkinje cells in distinct ways. The mossy fiber system carries afferent information from the spinal cord, brain stem, and cerebral cortex via pons and is responsible for moment-to-moment, rapid firing of Purkinje cells and then modulates ongoing movements. The climbing fibers relay information to the cerebellum from the inferior olivary nucleus which results in slow firing of Purkinje cells that seems to be important for motor learning.^[4]

Locomotive functions of cerebellum

The cerebellum has a crucial role in balance and locomotion. Functional specificity allows regions of the cerebellum to control aspects of motor control. These anatomical-functional relationships are discussed below.

- The medial zone of cerebellum: This zone integrates spinal and vestibular inputs and subsequently projects out through the fastigial nucleus to vestibulospinal and reticulospinal tracts. They appear to exert modulatory control of the rhythmic flexor and extensor locomotor pattern generated by vestibular and reticular nuclei. These connections also control extensor tone to maintain upright balance and stance. A lesion in this zone leads to a significant balance problem and impairment of postural tone.
- Intermediate zone (paravermal region): This zone receives input from the spine (via spinocerebellar tracts) and projects out through the globose and emboliform nuclei to the red nucleus and cerebral cortex. It integrates spinal and cortical inputs and influences locomotion through projections to motor cortical areas. The main function of this region is related to specific control of limb placement including timing, elevation and trajectory of limb elevation, and descent. Damage to this region leads to gait ataxia and swing phase overshoot of legs but no overt change in balance or postural tone.
- Lateral zone: This area receives input primarily from cerebral cortical area via pontine nucleus (corticopontocerebellar fibers) and projects out via the dentate nucleus through the red nucleus to the thalamus and cerebral cortical areas. This zone influences motor activities via cortical interactions and has an important role in voluntary modification of motor activities and the locomotor cycle. Lateral cerebellum is especially active in novel walking conditions where precise limb placement is necessary. It modulates visually guided motor activities because of the robust projection it receives from the visual cortex. A lesion in this region leads to limb ataxia and locomotion problems in novel and challenging situations. During uninterrupted walking, balance deficits contribute much more strongly to cerebellar gait ataxia (medial and intermediate zone) than do visually guided leg control deficits seen in the lateral zone.

Postural sway with a cerebellar lesion

Many of the cerebellar mechanisms are based on animal studies. But humans using bipedal locomotor mechanisms pose different challenges. Cerebellar damage in humans typically results in postural sway. Balance deficits as a result of lesion in midline cerebellar structures (vestibulocerebellum) lead to low frequency, high amplitude postural sway without a preferred direction and without intersegmental movements. On the other hand, in those with lesions in the intermediate zone (including anterior lobe), balance deficit is characterized by increased postural sway of high velocity and low amplitude; anteroposterior direction; postural tremor; and increased intersegmental movements of the head, trunk, and legs. Subjects with lesions in the lateral zone have only slight postural instability or sway.

Cerebellar control of voluntary movements

Cerebral cortical association areas plan voluntary movements and the plan is executed by the motor cortex. The motor cortex may act as a controller driving lower motor neurons in the brain stem and spinal cord. But there is a robust cerebellocerebral loop that modulates these motor functions. These loops connect the intermediate part of the cerebellum to the association cortex and the motor cortex. In turn, the outputs from the intermediate zone of the cerebellum converge down to meet the cerebral output at red nucleus and olive. Thus, both loop and parallel pathways exist between the cerebrum and cerebellum. The cerebellum influences voluntary activities through these pathways.

One of the major functions of the cerebellum is motor adaptation based on trial and error practice (error driven learning mechanism). That requires a memory mechanism that has activity-dependent modifiability. This memory mechanism is

considered to be located at the convergence of intrinsic cerebellar fibers (parallel fibers) and climbing fibers to the Purkinje cells. The process takes place through long-term depression (LTD), a characteristic form of synaptic plasticity occurring at parallel fiber-Purkinje cell synapses.^[5,6]

Hypermetria and decomposition of movements

Reaching movement requires multiple interacting torques working at the concerned joints. In cerebellar dysfunction, during reaching these torques have impaired control, which results in hypermetria. Decomposition of movement is a strategy of breaking down multijoint movements to compensate for impaired multijoint coordination.

Cognitive function of cerebellum

A closed cerebellocerebral loop is found in the prefrontal cortex and thus the cerebellum provides a forward model for mental functions in the cerebral cortex. This is analogous to already discussed cerebellocerebral loop concerned with motor functions. A primary cerebellar injury in premature infants has shown to be associated with contralateral decrease in cerebral volume.^[7] This strengthens the importance of the cerebellocerebral connections responsible for important cognitive functions.

A mental model of image, idea, or concept is formed in the temporoparietal association cortex. These already formed mental models are manipulated by the prefrontal cortex. After repeated exercise, the cerebellum copies a mental model to form an internal model through cerebello-cerebral loop. Because of this internal model formed by the cerebellum, we are able to conduct movements and thoughts unconsciously (processes occurring in the cerebellum are felt to not reach awareness). For this reason, an idea "just comes out of the blue" without an obvious conscious effort to think over it. This internal model hypothesis could also help explain delusions and hallucinations in schizophrenia.

Thus, the localization and regional distribution of pathology within the cerebellum dictates the clinical findings. Lesions of the midline cerebellar vermis produce truncal and gait ataxia, while involvement of the lateral cerebellar hemispheres produces a limb ataxia. Interruption of afferent and efferent connections within the neocerebellar system results in an ataxic gait (ie, swaying in the standing posture, staggering while walking with a tendency to fall, and the adoption of a compensatory wide base), scanning dysarthria, explosive speech, hypotonia, intention tremor (ie, oscillation of limbs that is pronounced at the end of a planned movement), dysdiadochokinesia (ie, impaired alternating movements), dysmetria (ie, impaired judgment of distance), decomposition of movement, and abnormalities of eye movements (ie, nystagmus).

Clinical phenotypes show considerable overlap; however, the genetic, molecular, and biochemical causes for these disorders are often distinct. Some phenotypes (dominant ataxias) show considerable genetic heterogeneity. These phenotypes may manifest with pure ataxia or involve multiple levels of the nervous system (including dementia, seizures, disturbance in proprioceptive function, movement disorders, and polmyoclonus).

Genetic-biochemical basis for classification

Early attempts to classify inherited ataxias were based on anatomic localization of pathologic changes (eg, spinocerebellar, pure cerebellar). In 1993, Harding introduced another classification in which the ataxias were placed into 3 categories, congenital, inherited metabolic syndromes with known biochemical defects, and degenerative ataxias of unknown cause.⁸ The last category was subdivided further into early onset (

Although ataxia is a prominent feature of all these disorders, the presentation can be variable (eg, static vs progressive, intermittent vs chronic, early vs delayed). The mode of inheritance also varies. Autosomal dominant, recessive, and nonmendelian inheritance patterns have been described. Nonmendelian inheritance patterns have become increasingly significant in the understanding of the biology of human diseases. The term refers to disorders of inheritance for which the rules of Mendelian genetics do not apply. Disorders of triplet repeat expansion and certain mitochondrial defects are examples of nonmendelian inheritance.

Clearly, a revision of the classification of hereditary ataxias is necessary to include current concepts. Such a classification system is obviously an evolving one, with a separate category that includes those disorders where the molecular basis is presently unknown. Selected conditions in each category are discussed below. The following outline includes clinical features and known information about gene products and known or putative function. Treatment options are only included where specific measures are available. The reader interested in the specifics of different conditions is referred to one of several excellent reviews on the subject in the Reference section.

Classification using a genetic-biochemical basis is as follows:

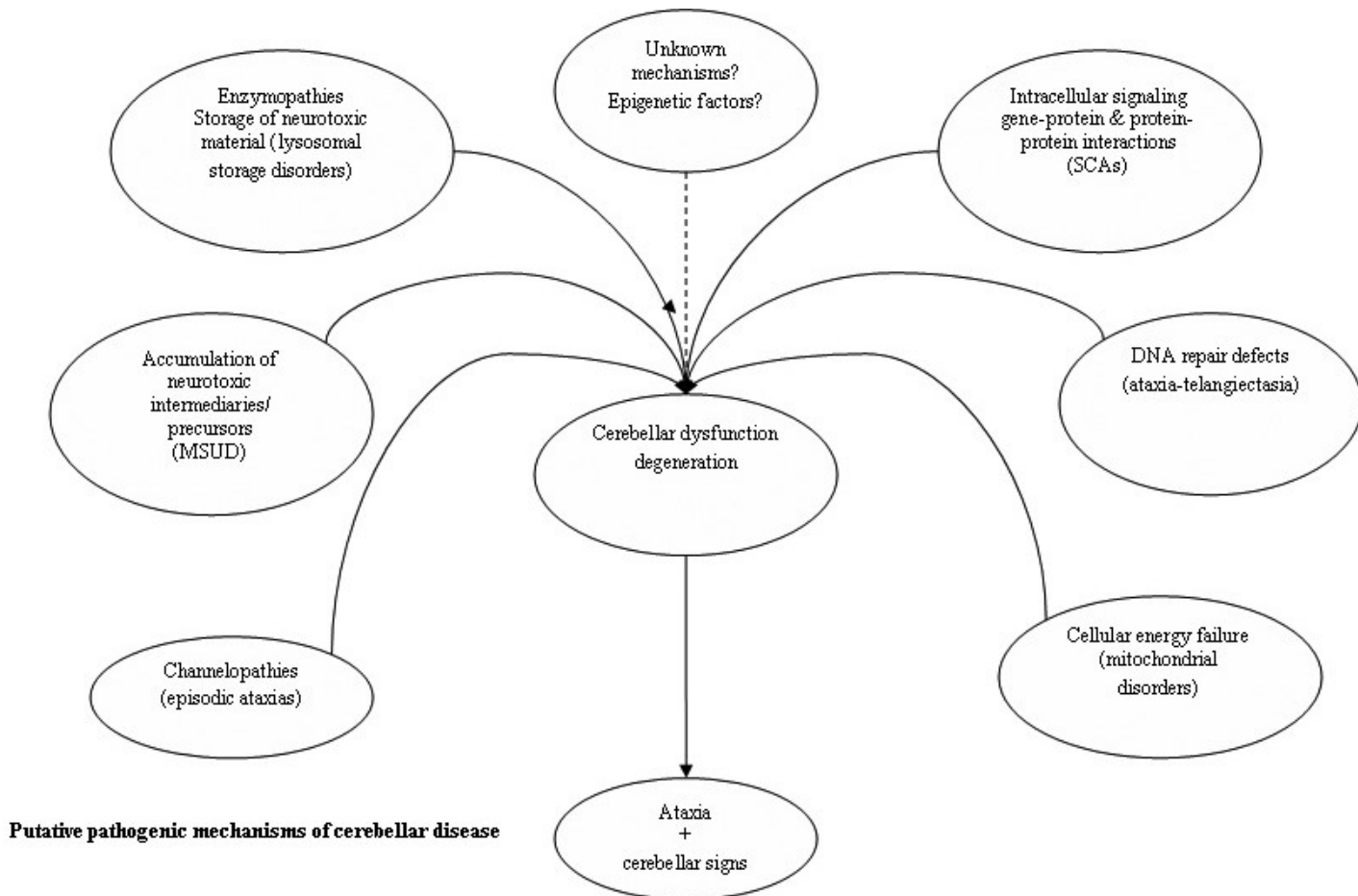
- Nonprogressive ataxias⁹
 - Pure congenital cerebellar ataxias with or without cerebellar hypoplasia
 - Autosomal recessive
 - Autosomal dominant
 - X-linked
 - Unknown
 - With posterior fossa malformations - Autosomal recessive (eg, Dandy Walker syndrome)
 - Congenital ataxia syndromes with cerebellar malformations
 - Autosomal recessive (eg, Joubert syndrome)
 - X-linked recessive (eg, X-linked congenital cerebellar hypoplasia and external ophthalmoplegia)
- Intermittent/episodic ataxias
 - Autosomal dominant - Channelopathies (eg, episodic ataxias [EA] 1, EA 2)
 - Autosomal recessive - Enzyme defects (eg, maple syrup urine disease [MSUD], urea cycle defects)
 - X-linked - Enzyme defects (eg, ornithine transcarbamylase [OTC] deficiency)
- Progressive ataxias with or without multisystem involvement
 - Autosomal dominant - Ataxias with spinocerebellar dysfunction
 - Triplet repeat disorders and polyglutamine accumulation (eg, SCAs 1-23, dentatorubropallidoluysian atrophy [DRPLA])
 - Autosomal recessive

- Triplet repeat disorders (eg, Friedreich ataxia)
 - Impaired DNA repair mechanisms (eg, xeroderma pigmentosum, Cockayne syndrome)
 - Enzyme defects (eg, Refsum disease, sphingolipidosis)
 - Protein misfolding (eg, spastic ataxia of Charlevoix-Saguenay)
- Maternal inheritance - Mitochondrial disorders (eg, neuropathy, ataxia, retinitis pigmentosa [NARP])
- Ataxias with polymyoclonus and seizures
 - Autosomal recessive
 - Dodecamer repeat expansions (eg, Baltic myoclonus)
 - Enzyme defects (eg, neuronal ceroid lipofuscinosis)
 - Maternal inheritance - Mitochondrial cytopathies (eg, myoclonic epilepsy with ragged-red fiber disease [MERRF])
- Other (unidentified mechanisms)
 - Angelman syndrome
 - Fragile X–related ataxia/tremor

In summary, the authors suggest a system of classification based on clinical features as the first distinction, mode of inheritance as the second distinction, and pathogenetic mechanisms as the third distinction. Although far from an ideal system, it serves to bring some order into a heterogeneous group of disorders. Clearly the classification is an evolving process because some disorders could be considered in more than one tier, eg, mitochondrial cytopathies can manifest with myoclonic epilepsy and ataxia, as well as chronic progressive ataxia as in the NARP syndrome.

Molecular Genetics and Putative Mechanisms of Cerebellar Disease

The mechanisms underlying disorders with cerebellar ataxia as a symptom reflect the diversity of etiologies that have been identified. For instance, genetic mutations affecting ion channel structure and function cause both intermittent and chronic symptoms^[10], and recessively inherited enzymopathies (enzyme deficiency) cause symptoms through accumulation of neurotoxic storage material and/or precursor metabolites. The understanding of mechanisms of neurodegeneration resulting in cerebellar disease has been influenced by discoveries in the molecular genetics of nontraditional inheritance patterns underlying conditions such as SCAs and mitochondrial disorders. Therefore, special aspects of molecular genetics and putative mechanisms of cerebellar disease are discussed together (see Media file 1).



Putative pathogenic mechanisms of cerebellar disease.

Triplet repeat expansions

This class of mutation is characterized by dynamic expansion of tandem nucleotide repeats in the human genome. These stretches of repeats tend to be inherently unstable, and this instability favors expansion. When the length of the repeat expansion exceeds the range in the general population, a symptomatic state may result. These mutations help explain clinical observations of increasing severity of symptoms and an earlier age of onset in successive generations seen with several of the dominantly inherited disorders—a phenomenon termed genetic anticipation. Such dynamic mutations form the basis of an increasing list of inherited neurologic disorders that includes mental retardation (fragile X syndrome), myotonic dystrophy, oculopharyngeal muscular dystrophy, Friedreich ataxia, Huntington disease, and the dominantly inherited cerebellar ataxias.

The trinucleotide expansion of cytosine, adenine, and guanine (CAG) repeats is translated into a polyglutamine tail, a common feature of several of the dominantly inherited ataxias. The expansion above a critical threshold, which appears to be different for each SCA type, determines presence of disease. The causative proteins for each type bear no homology to other known proteins or to each other apart from the polyglutamine tail. The polyglutamine tails themselves appear to be toxic once a disease-specific threshold is reached, and this central feature suggests a final common pathway.

The pathogenic mechanism(s) underlying cerebellar disease appear to involve proteolytic cleavage and nuclear accumulation of toxic products. Such proteolytic cleavage by releasing toxic fragments containing an expanded polyglutamine tail, may serve to further facilitate entry of cytoplasmic polyglutamine proteins to the nucleus. Secondary processes for neuronal injury likely involve downstream effects of apoptotic activation, accumulation, misfolding, aggregation, and sequestration of other proteins such as transcription factors and chaperones, leading to dysfunction of proteins and their intranuclear or intracellular accumulation. The putative disease mechanisms involved in the SCAs can be categorized into the following:

- Transcriptional abnormalities (SCA17 and SCA7): Ataxins appear to function as transcriptional regulators, and the interaction with polyglutamine proteins results in an impairment of transcription. At other times, transcription factors may be sequestered into the polyglutamine aggregates, leading to transcriptional shutdown and neuronal death.
- Calcium signaling defects (SCA6 and SCA14): In SCA6, the expanded CAG repeat is within a gene coding for the alpha subunit of the voltage-gated calcium channel. The polyglutamine aggregates in this disorder are cytoplasmic, and altered channel function may be responsible rather than a toxic gain in function.
- Phosphorylation defects (SCA12 and SCA14): In these disorders, protein phosphorylation mediated through specific enzymes belonging to serine/threonine phosphatase (SCA12) and serine threonine kinase (SCA14) families is affected. A wide variety of cellular signaling pathways where these function as second messengers can be secondarily affected.
- Defective ubiquitination and proteosome function (SCA3): Protein handling and clearance in the cell is affected through the ubiquitin-proteosome pathway. Components of this pathway may get sequestered in the polyglutamine aggregates, leading to a perturbation in cellular protein homeostasis.
- Protein misfolding and chaperone defects: Protein folding and structure are vital to normal function; chaperone proteins facilitate this folding properly. Dysfunction of chaperone proteins may contribute to protein misfolding. Such a process may underscore the pathogenic mechanism in SCA1, in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), and in the leukoencephalopathy associated with vanishing white matter (VWM).

Mitochondrial DNA defects^[11]

Since mitochondria were established to carry unique functions through their own functional genome, a new mechanism of nonmendelian inheritance, maternal inheritance, was discovered. All the mitochondria in the newly formed zygote are derived from the ovum (ie, maternally derived). Mitochondrial disorders can result from defects of mitochondrial proteins, either coded by the nuclear or by the mitochondrial DNA (mt DNA). Mitochondrial DNA is more vulnerable to mutations in the oxidizing environment of mitochondria because its repair mechanisms are poor compared to nuclear DNA. Mutations in mitochondria accumulate in cells until a threshold is reached. Eventually, the proportion of mutant mitochondria exceeds wild type, resulting in the manifestation of impaired cell function.

The process of uneven replicative segregation ensures different proportions of mutant and wild types in different tissues, a condition termed heteroplasmy. Mildly-to-moderately deleterious mutations can persist and be transferred to offspring. The differential segregation and production of reactive oxygen species can vary among tissues and organ systems in affected individuals, giving rise to varying phenotypes.

Postmitotic cells such as neurons appear to carry higher ratios of mutant mitochondrial DNA, which thereby confer vulnerability to metabolic stress. This vulnerability may show a regional variation within the different regions of the brain, thereby partially explaining the variable patterns of neurologic involvement in many mitochondrial disorders. Some of the examples of mitochondrial disorders manifesting with ataxia include Friedreich ataxia (GAA repeat expansion-nuclear), MELAS syndrome ([mitochondrial myopathy, encephalopathy, lactic acidosis, stroke syndrome] A3243-G mutation-maternal), ataxia with selective vitamin E deficiency (AVED), and X-linked ataxia with sideroblastic anemia.

DNA repair defects

Mutations in proteins involved in repairing DNA breaks seem to provide yet another pathway resulting in disorders with ataxia (eg, ataxia-telangiectasia, ataxia with oculomotor apraxia types 1 and 2, SCA with sensory neuropathy [SCAN1]). The ataxia-telangiectasia mutated (ATM) protein functionally belongs to a family of protein kinases with the critical role of rapidly healing DNA breaks. Mutations in this protein cause ataxia-telangiectasia. Aprataxin, a histidine triad protein is involved similarly in single-stranded DNA repair, while senataxin is involved in splicing and termination of tRNA and may also function as a DNA helicase.

Nonprogressive Cerebellar Ataxias

This group includes diverse conditions that manifest either at birth or in early life. A structural abnormality in the form of cerebellar hypoplasia with or without other posterior fossa malformations affecting the brainstem structures may or may not be demonstrable. Because of the complex maturational and myelination processes within the brain that are age related, the clinical presentation of these disorders in early life is marked by symptoms other than ataxia. Most often hypotonia and developmental delays are striking. Ataxia is only recognized when efforts at independent walking are unsuccessful. In early life, considerable overlap of the neurologic phenotype occurs.

The classification of nonprogressive ataxias is challenging. At the risk of oversimplification, the hereditary nonprogressive ataxias may be categorized as the following:

- Pure congenital cerebellar ataxias
- Cerebellar ataxias associated with posterior fossa malformations
- Congenital ataxic syndromes
- Ataxic syndromes without cerebellar malformations

The principal differential diagnosis needs to include metabolic and neurodegenerative conditions manifesting in early life discussed in this article. The suggested metabolic testing and neuroimaging studies can help distinguish this category from other hereditary conditions that are progressive in nature.

A long list of conditions is reported featuring ataxia in association with other clinical features. A few conditions such as Gillespie syndrome include 1 or 2 additional features (eg, mental retardation, partial aniridia), while other conditions such as Joubert syndrome (ie, hypotonia, hyperventilation, facial dysmorphism, retinal dystrophy, renal involvement) and COACH syndrome (ie, cerebellar hypoplasia, oligophrenia, ataxia, coloboma, hepatic fibrosis) feature malformations in multiple organ systems.

Inheritance patterns are usually autosomal recessive or X linked depending on the syndrome. In the case of Joubert syndrome, evidence for genetic heterogeneity exists. Currently, mutations in 9 different genes are known to be associated with a Joubert syndrome phenotype.

Table 1. Nonprogressive Congenital Ataxias

Disorder/Syndrome	Phenotype*	Inheritance
NPCA with or without cerebellar hypoplasia	Early hypotonia Delayed motor and speech development	Autosomal recessive Autosomal dominant X linked recessive Sporadic
NPCA with posterior fossa malformations (eg, Dandy Walker syndrome)	Variable association with hydrocephalus Delays in motor development Cognitive delay	N/A
Ataxia syndromes, multiple congenital anomalies, and cerebellar hypoplasia (eg, Joubert syndrome, Varadi syndrome, COACH syndrome)	Encephalo-oculo-hepato-renal anomalies with recognized association patterns of anomalies	Autosomal recessive Autosomal dominant X linked
Ataxia syndromes with cerebellar hypoplasia (eg, Gillespie syndrome)	Partial aniridia Hypogonadotrophic hypogonadism External exophthalmoplegia	Autosomal recessive

*Gait ataxia is a constant feature.

Clinical features

- Early hypotonia
- Developmental delay
- Feeding difficulties and oromotor dysfunction
- Speech delay secondary to articulatory difficulties
- Cognitive difficulties (may be recognized at a later age)
- Specific pattern of inheritance upon genetic assessment of the family

Laboratory findings

- Genetic mutation tests: These are available only in selected conditions, eg, certain forms of Joubert syndrome. Testing is available for at least 4 of the causative genes in which mutations appear in Joubert syndrome: *AHI1*, *CEP290*, *NPHP1*, and *TMEM67*. Gillespie syndrome is known to be associated with mutations in the *PAX6* gene.
- Metabolic screening: Results are negative.
- Neuroimaging studies: MRI is superior because it permits better visualization of the posterior fossa. Variable degrees of hypoplasia of the cerebellar vermis are reported. In more severe cases, the entire vermis may be absent, and associated abnormalities are noted in the cerebellar hemispheres. However, in mild cases, the cerebellum is morphologically normal on imaging studies. Associated abnormalities of the brainstem and supratentorial structures may be of additional value in the diagnosis of syndromes such as Dandy Walker malformation. In Joubert syndrome, a characteristic neuroimaging finding of the "molar-tooth" sign is helpful.

Intermittent or Episodic Ataxias

Channelopathies^[12]

Channelopathies represent a number of neurologic disorders that manifest with symptoms of an episodic or transient nature. The underlying molecular defect affects the functioning of a voltage-gated ion channel, thereby altering membrane excitability in neurons. External stimuli often trigger symptoms or episodes. Clinical and genetic heterogeneity is evident in the episodic ataxias with up to 6 additional forms currently recognized. So far the mutations appear to involve ion channel subunits.

Episodic ataxia 1^[13,14]

- Gene, inheritance, and pathogenesis: EA1 is a rare autosomal dominant disorder and represents a channelopathy. It is caused by point missense mutations that affect the human voltage-gated potassium channel (*KCNA1* gene on band 12p13). This channel is widely expressed, but is especially prominent in the cerebellum. The mutation can impair channel function by reducing the amplitude of the potassium current and by altering its voltage-dependent kinetics.
- Clinical features
 - Continuous myokymia between attacks
 - Duration of seconds to minutes
 - Partial epilepsy (some individuals in affected families)
 - Sudden episodes of ataxia precipitated by movement, startle, or emotion
- Laboratory findings

- Electroencephalography (EEG) may show continuous rhythmic muscle discharge artifact, which may become more prominent with hyperventilation.
- Electromyography is the only helpful investigation; it usually demonstrates continuous motor unit activity in all patients.
- Treatment: Partial responses to acetazolamide, carbamazepine, phenytoin, and phenobarbital have been reported.

Episodic ataxia 2^[13]

- Gene, inheritance, and pathogenesis: EA2 is an autosomal dominant disorder that has been associated with mutations that affect the calcium channel (*CACNA1A*^[15]) gene at the 19p13 locus. It is allelic to familial hemiplegic migraine and SCA6, wherein mutations affecting the same gene have been described. Haploinsufficiency may underlie the EA2 pathogenesis because the majority of the mutations causing EA2 result in nonfunctional calcium channels. EA2 exhibits incomplete penetrance and variable expressivity both between and within families.
- Clinical features
 - Headache (in some families)
 - Intermittent midline cerebellar dysfunction characterized by bouts of ataxia, nystagmus, dysarthria, and vertigo
 - Absence of myokymia
 - Provoking factors - Stress, exercise, and fatigue, among others
- Laboratory findings: *CACNA1A* gene mutation testing is available in certain laboratories.
- Treatment: A few patients with EA2 may respond to acetazolamide

Episodic ataxia 3

- A clinically distinct form of autosomal dominant episodic ataxia occurs in the Canadian Mennonite population. The candidate gene maps to a 4 cM region on chromosome 1q42 between markers D1S2712 and D1S2678. No mutations have been identified to date.
- Clinical features
 - Variable age of onset
 - Vestibular ataxia, vertigo, tinnitus, and interictal myokymia
 - Symptoms triggered by sudden movement, stress, exertion, and fatigue
- Laboratory findings: No gene tests are available.
- Treatment: The condition responds well to acetazolamide.

Table 2. Episodic ataxias

Disorder/Syndrome	Phenotype*	Inheritance	Gene Locus	Gene Product/Biochemical Defect
EA1	Intermittent	Autosomal	12q13	Missense point mutations

	ataxia	dominant		affecting the voltage-gated potassium channel (<i>KCNA1</i>)
EA2	Intermittent ataxia	Autosomal dominant	19q13	Point mutations or deletions allelic with SCA6 and familial hemiplegic migraine Altered calcium channel function
EA2	Intermittent ataxia	Autosomal dominant	2q22-q23	Voltage-dependent L-type calcium channel, beta subunit
EA3	Intermittent ataxia with vertigo and tinnitus	Autosomal dominant	1q42	Not identified

Inherited Enzyme Defects

Maple syrup urine disease (intermittent form)^[16,17,18,19,20]

A delayed presentation of this autosomal recessive form of a branched chain aminoacidopathy may occur at any age from infancy to adulthood.

- Gene, inheritance, and pathogenesis: This is an autosomal recessive disorder caused by a deficiency of branched chain alpha keto acid dehydrogenase complex. Mutations of at least 4 gene loci are known to result in this condition, including 19q13.1-q13.2 and 7q31.
- Clinical features
 - Characteristic urine odor of maple syrup, as well as in other body fluids and earwax
 - Intermittent bouts of ataxia and neurologic obtundation progressing to coma
 - Possibly, mental retardation and motor delay in intermediate form
- Laboratory findings
 - Elevation of branched chain amino acids and branched chain keto acids in the urine, plasma, and cerebrospinal fluid (CSF)
 - Metabolic acidosis, ketonemia, and ketonuria; occasional hypoglycemia and hypoalaninemia
 - L-alloisoleucine in body fluids (pathognomonic)^[21]
 - Assay of branched chain keto acid dehydrogenase activity in skin fibroblasts
 - Mutation testing
- Treatment^[22]
 - Treatment includes restriction of dietary protein intake and supplementation of branched chain amino acid-free synthetic formula to meet protein and other dietary needs.

- Begin thiamine supplementation in thiamine-responsive individuals (5-20 mg/kg/d, not to exceed 100 mg/d) immediately. In adults, 100 mg may be administered immediately in the acute situation, followed by further supplementation of 50-100 mg/d until adequate oral intake and a stable clinical state are achieved.

Hartnup disease^[23,24]

The incidence based on neonatal screening data is estimated at 1 in 30,000. The reduced availability of tryptophan may lead to a secondary deficiency of the vitamin niacin (nicotinic acid).

- Gene, inheritance, and pathogenesis: The locus associated with Hartnup disease is 5p15. This autosomal recessive disorder is caused by defective intestinal transport and renal tubular reabsorption of neutral amino acids (primarily tryptophan). Hartnup disorder is caused by mutations in the gene encoding the neutral amino acid transporter SLC6A19. SLC6A19 is a sodium-dependent and chloride-independent neutral amino acid transporter, expressed predominately in kidney and intestine.
- Clinical features
 - Intermittent ataxia and other cerebellar signs
 - Neuropsychiatric dysfunction ranging from emotional lability to frank psychosis
 - Pellagralike skin rash induced by exposure to sunlight
 - Normal intelligence and no abnormal neurologic signs in most patients with the biochemical phenotype
- Laboratory findings
 - Excessive excretion of monoamino-monocarboxylic amino acids in urine
 - Urinary indoxyl derivatives (5-hydroxyindoleacetic acid) detectable in urine following an oral tryptophan load
- Treatment: Treatment includes a high-protein diet. Niacin supplementation reverses the skin and neuropsychiatric manifestations. A tendency exists for spontaneous improvement.

Pyruvate dehydrogenase deficiency

- Gene, inheritance, and pathogenesis: The commonest form of pyruvate dehydrogenase (PDH) deficiency is an X-linked recessive disorder that affects a mitochondrial multienzyme complex, which is involved in the conversion of pyruvate to acetyl-CoA. The *PDHA1* gene codes for 3 enzymes of the PDH complex. The E1 alpha1 subunit of this complex is most often affected. Inheritance is X linked for the latter form. A high proportion of heterozygous females manifest severe symptoms (in the X-linked form).
- Clinical features
 - Many present in early infancy with a catastrophic neurologic picture of hypotonia, lactic acidosis, and seizures (associated with cerebral malformations).
 - About 30% present with facial dysmorphic features, including microcephaly, narrow head, frontal bossing, long philtrum, episodic ptosis, abnormal eye movements, wide nasal bridge, upturned nose, and flared nostrils.
 - A benign late-infantile variant can occur.
 - Episodic ataxia is characteristic.
 - Uncommonly, mental and motor development is normal.

- Fatigue is noticed after exercise.
- Transient paraparesis is a feature.
- Laboratory findings
 - Serum and CSF lactic acidosis is characteristic. The lactate-to-pyruvate ratio is normal.
 - PDH activity in skin fibroblasts is reduced.
 - Mutation testing is available in certain laboratories only.
 - In the prenatal and early infantile form, multiple areas of necrosis in the gray matter, white matter, and basal ganglia are noted on imaging studies.
 - Limited information is available concerning late benign presentations of this disorder. Postmortem and autopsy in one affected male who died at age 50 years showed findings of cerebellar degeneration and lesions around the third ventricle and cerebral aqueduct. This case suggests findings that overlap with Leigh disease and Wernicke encephalopathy.
- Treatment
 - Thiamine supplementation in high doses (5-20 mg/kg/d, not to exceed 100 mg/d in acute stage) may be effective in the thiamine-responsive form of the disease.
 - A ketogenic diet has been effective in some patients.
 - Treatment of lactic acidosis by dichloroacetate may be helpful. Administer 2 doses of dichloroacetate (50 mg/kg body weight) separated by 2 hours. If the level does not drop 20% below baseline after 6 hours, the patient is considered a nonresponder. For a partial response of less than 20% of baseline levels but above 5 $\mu\text{mol/L}$, 2 additional doses may be tried. Published open trials on dichloroacetate indicate improved survival (with reduced morbidity) in responders. However, questions remain regarding the efficacy of this treatment. Long-term side effects of peripheral neuropathy associated with this therapy are reported.

Pyruvate carboxylase deficiency

Pyruvate carboxylase (PC) is a nuclear-encoded mitochondrial enzyme that catalyzes the conversion of pyruvate to oxaloacetate. PC deficiency can be categorized into 3 types. Type A, found in North American Indians, involves lactic acidosis and psychomotor retardation. Type B, found in France and the United Kingdom, has a severe phenotype with hyperammonemia. Patients with type B die by age 3 months.^[25] Type C manifests with relatively benign intermittent ataxia, and affected individuals may have normal development. PC deficiency usually manifests in the neonatal period with severe lactic acidosis or in early infancy with features similar to PDH deficiency with psychomotor retardation, hypotonia, and seizures.

- Gene, inheritance, and pathogenesis: The most common disorder of pyruvate metabolism is an autosomal recessive inherited deficiency of PC. Identified mutations affect the gene locus on chromosome 11 (11q13.4-q13.5). Common founder 1828G-->A missense mutation has been described in Ojibway-Cree patients in Manitoba.^[26]
- Laboratory findings
 - Lactic acidosis (elevated plasma lactate)
 - Increased lactate-to-pyruvate ratio
 - Elevated blood levels of ammonia, citrulline, proline, and lysine in type B (French form)

- Reported abnormality on ultrastructural examination of skeletal muscle in the neonatal form: Subsarcolemmal aggregation of lipid droplets, glycogen granules, and pleomorphic mitochondria is found. Although nonspecific, these findings in combination with age of onset, clinical features, and lactic acidosis are often helpful in diagnosis.
- Cystic periventricular white matter changes in the neonatal form on magnetic resonance imaging (MRI)
- Assay for enzyme activity in cultured fibroblasts
- Mutation testing
- Treatment: Options are limited to symptomatic treatment of lactic acidosis and are similar to those employed for the treatment of PDH deficiency. Biotin and aspartate have been used in selected patients. Prognosis remains poor for types A and B.

Defects of mitochondrial fatty acid beta-oxidation^[27]

- Gene, inheritance, and pathogenesis: Recessively inherited defects that affect mitochondrial beta-oxidation can result in intermittent episodes of neurologic symptoms (eg, weakness, ataxia, coma) in affected individuals. Defective fatty acid oxidation carries with it the consequence of energy deficit in the nervous system. The results are reflected in diffuse CNS dysfunction in situations of metabolic decompensation, such as that which accompanies prolonged fasting. Examples of such defects are as follows:
 - Carnitine palmitoyltransferase-1 deficiency
 - Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)
 - Multiple-acyl-CoA dehydrogenase deficiency (glutaric aciduria type II)
 - Primary systemic carnitine deficiency
 - Short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
 - Short-chain acyl-CoA dehydrogenase deficiency
 - Trifunctional enzyme deficiency
 - Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
- Clinical features
 - Episodic vomiting
 - Intermittent bouts of weakness, lethargy, ataxia, and coma
 - Neurologic symptoms induced by fasting
- Laboratory findings
 - Hypoglycemia with minimal-to-absent ketonemia and ketonuria
 - Mild lactic acidosis, hyperammonemia
 - Reduced plasma carnitine levels (free and total) in many fatty acid oxidation disorders
 - Increased dicarboxylic aciduria (suberic, sebamic, adipic acids) upon urinary organic acid analysis
 - Characteristic acylcarnitine profiles and urinary acyl-glycines associated with specific disorders of fatty acid oxidation
 - Specific enzyme assays on cultured skin fibroblasts
 - Mutation analysis (eg, the common A985G mutation in MCADD)
- Treatment

- Avoidance of prolonged fasting
- Carnitine supplementation in doses of 50-100 mg/kg/d divided into 3 doses
- Adequate caloric intake through intravenous glucose during acute presentations
- Substitution of dietary fat with medium-chain triglycerides (may be helpful in bypassing metabolic block in VLCAD)
- Corn starch feeds prior to bedtime (may help prevent hypoglycemia)

Urea cycle defects (late onset)^[28]

- Gene, inheritance, and pathogenesis: Defects of each of the 5 enzymes of the urea cycle and 1 of its activators have been described. Most manifest with hyperammonemic coma in the neonatal period. Partial deficiencies can result in delayed presentation or intermittent symptoms during periods of decompensation. Elevated ammonia is poorly handled within the nervous system because of its ability to cross the blood-brain barrier. Secondary excitotoxicity related to release of glutamate and free radical-induced injury lead to diffuse cerebral dysfunction. Four of the 5 enzyme deficiencies (except ornithine transcarbamylase) are inherited as autosomal recessive defects. The 5 urea cycle enzymes are as follows:
 - Carbamyl phosphate synthetase
 - Ornithine transcarbamylase (X-linked inheritance)
 - Argininosuccinate synthetase
 - Argininosuccinate lyase
 - Arginase
- Clinical features: Delayed presentations of partial enzyme deficiencies in children and adults include the following:
 - Behavioral abnormalities such as self-abusive behavior
 - Episodic hyperammonemia
 - Intermittent ataxia and spasticity
 - Protein intolerance with intermittent vomiting
 - In adults, migrainelike episodes, confusional states, visual impairment, hallucinations, and neuropsychiatric symptoms
 - Presentation in ornithine transcarbamylase heterozygotes during pregnancy
 - Hyperactive deep tendon reflexes, papilledema, and decerebrate or decorticate posturing
 - Arginase deficiency clinically similar to spastic diplegic cerebral palsy^[29]
- Laboratory findings^[30]
 - Respiratory alkalosis
 - Elevated plasma ammonium (ionized form at physiologic pH)
 - Abnormalities in plasma amino acids
 - Elevated glutamine and alanine in blood and CSF
 - Indication of precise urea cycle enzyme deficiency possible by presence or absence of citrulline, argininosuccinic acid in plasma, and orotic acid in urine
 - Enzyme assays on tissue from liver biopsy
 - DNA analysis (can be confirmatory and is less invasive)

- Treatment
 - Reduction of dietary protein intake with special dietary formulas
 - Supplementation of arginine and/or citrulline (depending on site of urea cycle defect)
 - Aggressive treatment of hyperammonemic coma using alternative pathway activation (eg, via sodium benzoate, sodium phenylacetate, and arginine)
 - Orthotopic liver transplant (another therapeutic option)
 - Gene therapy for OTC deficiency (remains experimental)

Table 3. Intermittent Ataxias Related to Enzyme Defects

Disorder/Syndrome	Phenotype*	Inheritance	Gene Locus	Gene Product/Biochemical Defect
Maple syrup urine disease	Intermittent ataxia	Autosomal recessive	19q13.2	Mutations affect the E1 alpha subunit of branched-chain alpha-keto dehydrogenase complex that catalyzes the conversion of alpha keto acids to acyl-CoA and carbon dioxide
Hartnup disease	Intermittent ataxia	Autosomal recessive	11q13	Abnormality in the intestinal and renal transport of neutral alpha amino acids
Pyruvate dehydrogenase deficiency	Intermittent ataxia Lactic acidosis	X-linked recessive	Xp22.2-p22.1	Defective E1 component of the PDH complex
Pyruvate carboxylase deficiency	Intermittent ataxia Lactic acidosis	Autosomal recessive	11q13.4-q13.5	N/A
Defects of mitochondrial fatty acid beta-oxidation	Intermittent ataxia Metabolic	Autosomal recessive	N/A	Multiple defects affecting different acyl-CoA

	acidosis Elevated ammonia			dehydrogenases
Late-onset urea cycle defects	Intermittent ataxia	Autosomal recessive	7q21.3-q22 (arginosuccinate lyase)	N/A
Argininosuccinic acidemia	Episodic encephalopathy		2q33-q36 (carbamoyl-phosphate synthetase I)	
Carbamyl phosphate synthetase deficiency			9q34 (arginosuccinate synthetase)	
Citrullinemia			Xp21.1 (ornithine carbamoyltransferase)	
Ornithine transcarbamoylase deficiency			6q23 (arginase)	
Argininemia				

Chronic or Progressive Ataxias

The following disorders are dominantly or recessively inherited. They manifest primarily with ataxia and cerebellar dysfunction, which are chronic and may be progressive with or without the presence of other neurologic abnormalities. This group of disorders is large; many have been associated with molecular genetic abnormalities, linking them to identifiable biochemical defects. DNA-based laboratory testing is available for many of these disorders. SCAs 1, 2, 3, 6, and 7, and dentatorubropallidoluysian atrophy (DRPLA) are caused by dynamic mutations that affect tandem triplet nucleotide repeats. The salient phenotypic features and the degree of triplet repeat expansions necessary to produce pathologic symptoms are summarized in the tables accompanying this discussion.

Dominantly Inherited Ataxias

The number of dominantly inherited SCAs that have been described has increased to 29 and are labeled SCA1 onwards in sequence. SCA9 refers to a hitherto unknown variety, while SCA24 describes a recessively inherited SCA with saccadic intrusions. The genetic basis for most of these disorders is related to expansion of triplet nucleotide repeats. (See the tables for a summary of the gene loci and putative mechanisms related to these disorders). A great degree of overlap in phenotype is noted, including the age of onset, with the major group of symptoms related to cerebellar and spinocerebellar pathway dysfunction. Other than distinguishing features described in selected cases, findings from neuroimaging studies are relatively nonspecific. Most of the triplet expansions affect CAG repeats; in the SCA8 form, an untranslated CTG expansion is involved.

A slowly progressive cerebellar syndrome with various combinations of oculomotor disorders, dysarthria, dysmetria/kinetic tremor, and ataxic gait are key presenting features. In addition, pigmentary retinopathy, extrapyramidal movement disorders (parkinsonism, dyskinesias, dystonia, chorea), pyramidal signs, cortical symptoms (seizures, cognitive impairment/behavioral symptoms), and peripheral neuropathy are also noted.

The following selected clinical features are often helpful in predicting association with a gene defect:

- SCA2 - Slowing of saccades
- SCA1, SCA2, and SCA3 - Ophthalmoplegia
- SCA1, SCA2, SCA3, SCA4, SCA8, SCA18, and SCA25 - Associated signs of peripheral neuropathy
- SCA7 - Pigmentary retinopathy
- SCA3 - Spasticity
- SCA17 and DRPLA - Cognitive impairment/behavioral symptoms
- SCA27 - Associated with dyskinesias
- SCA10, SCA17, and DRPLA - Seizures

Three patterns of atrophy are described on brain MRI: pure cerebellar atrophy, olivopontocerebellar atrophy, and global brain atrophy. The presence of dentate nuclei calcifications in SCA20 can result in a hypointense/low signal on certain brain MRI sequences. Several identified mutations correspond to expansions of repeated trinucleotides (CAG repeats in SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, and DRPLA; CTG repeats in SCA8). A pentanucleotide repeat expansion (ATTCT) is associated with SCA1.

The following is a discussion of a few of the dominantly inherited ataxias in which the gene product and its role in the pathogenesis has been identified. Most of the SCAs are accounted for by the SCA1, SCA2, SCA3, SCA6, SCA7, and SCA8 subtypes; the remaining types are rare and have been reported in few families or in specific ethnic backgrounds. Treatment, for the most part, is restricted to the use of pharmacologic agents for targeted symptoms, such as the use of 5 hydroxytryptophan and acetazolamide for ataxia, amantadine/levodopa/dopamine agonists in SCA2-SCA3, and the use of tizanidine/baclofen for spasticity. Deep brain stimulation has been used for the treatment of tremor in SCA2.

Spinocerebellar ataxia 1

- Clinical features
 - Onset in the fourth decade of life
 - Gait ataxia, dysarthria, dysmetria, nystagmus, muscle wasting, and dystonia in late stages of the disease
 - Gain of function mutation, resulting in a protein (ataxin-1)

Spinocerebellar ataxia 2

- Clinical features
 - Age of onset from 2-65 years
 - Ataxia, facial fasciculation, lid retraction, and reduced ocular saccadic velocity

- SCA2 protein product termed ataxin-2

Spinocerebellar ataxia 3

The disorder is allelic to Machado-Joseph disease, which affects individuals of Portuguese-Azorean descent.

- Clinical features
 - Age of onset after the fourth decade of life
 - Ataxia, pyramidal and extrapyramidal signs, amyotrophy, facial and lingual fasciculations, ophthalmoplegia, and exophthalmos
 - Protein product termed ataxin-3

Spinocerebellar ataxia 4

- Clinical features
 - Late-onset ataxia, sensory axonopathy
 - Symptoms beginning in second to fourth decade of life
 - Pathologic examination findings demonstrating degeneration of cerebellar Purkinje cells, dorsal root sensory ganglion neurons, and ascending posterior columns

Spinocerebellar ataxia 5

- Clinical features
 - Cerebellar ataxia, facial myokymia, impaired vibration sense, and very slow progression
 - Age of onset variable, with a mean age of 37 years (10-68 y)
 - First family described descending from Abraham Lincoln's grandparents; second family described in northeastern France

Spinocerebellar ataxia 6

- Clinical features
 - Ataxia, nystagmus, dysarthria, and loss of vibration and joint position sense
 - Pathologic examination showing loss of Purkinje cells, granule cells, neurons of the inferior olive nucleus, and dentate nucleus
 - Progressive pancerebellar dysfunction without involvement of cognitive, pyramidal, or extrapyramidal function
 - Slow progression over 20-30 years
 - Symptoms beginning in the fourth or fifth decade of life

Spinocerebellar ataxia 7

- Clinical features
 - Ophthalmoplegia, dysarthria, pyramidal and extrapyramidal signs, and impaired vibration sense

- Visual loss due to macular retinal degeneration (unique finding in this disorder)

Spinocerebellar ataxia 8

- Clinical features
 - Onset of symptoms ranging from age 18-65 years, with a mean of 39 years
 - Dysarthria and gait instability (commonly initial symptoms)
 - Examination findings including spastic dysarthria, nystagmus, limb spasticity, limb and gait ataxia, and diminished vibration perception
 - Progression generally slow

Spinocerebellar ataxia 10

- Clinical features
 - Onset in third to fifth decade of life
 - Pure cerebellar ataxia, nystagmus, dysarthria, dysphagia, hypotonia, and generalized and/or complex partial epilepsy

Spinocerebellar ataxia 11

- Clinical features
 - Mild disorder, with pure ataxia as a major feature
 - Normal life span with mean age of onset of 30 years (15-70 y)
 - Retained capacity for ambulation

Spinocerebellar ataxia 12

- Clinical features
 - Tremor in early stages
 - Later development of a pure SCA

Spinocerebellar ataxia 14

- Clinical features
 - Progressive cerebellar ataxia
 - Dysarthria
 - Myoclonus (rare)
 - Facial myokymia
 - Hyperreflexia
 - Cerebellar atrophy

Spinocerebellar ataxia 17

- Clinical features
 - Progressive ataxia
 - Dysmetria
 - Dementia
 - Bradykinesia
 - Hyperreflexia

Spinocerebellar ataxia 27

- This disorder presents with distinct clinical features, described initially in a Dutch kindred, with autosomal dominant inheritance.
- Clinical features
 - Early onset tremor, ataxia in the second decade, and orofacial dyskinesias
 - Aggressive behavioral outbursts

Dentatorubropallidoluysian atrophy

- Gene, inheritance, and pathogenesis: The condition is allelic to the Haw River syndrome reported in blacks. Pathologic features include nerve cell loss and gliosis affecting the dentate nucleus, red nucleus, pallidum, and subthalamic nucleus of Luys. The age of onset varies. It has been reported in Japan and Europe.
- Clinical features
 - Ataxia
 - Dementia
 - Polymyoclonus
 - Chorea
- Laboratory findings
 - Imaging studies demonstrate spinocerebellar atrophy and varying degrees of multisystem atrophy.
 - Diagnosis rests on molecular DNA confirmation of expansion of the number of CAG repeats. Molecular genetic testing is available for SCA types 1, 2, 3, 6, 7, and DRPLA.

Table 4. Dominantly Inherited Chronic/Progressive Ataxias

Autosomal Dominant Ataxias	Neurologic Phenotype (Gait ataxia is a constant feature)	Triplet Repeat Size	Gene Locus/Gene Product
Spinocerebellar ataxia (SCA1)	Peripheral neuropathy Pyramidal signs	CAG expansion 39-83 (6-36 normal range)	6p23 Ataxin-1

	Ophthalmoparesis		(ATXN1)
Spinocerebellar ataxia (SCA2)	Abnormal ocular saccades Hyporeflexia Dementia Peripheral neuropathy, less frequent Extrapyramidal findings	CAG expansion 34-400 (15-31 normal range)	12q24.1 Ataxin-2 (ATXN2)
Spinocerebellar ataxia (SCA3/MJ disease)	Pyramidal, extrapyramidal, and ocular movement abnormalities Amyotrophy Sensory neuropathy	CAG expansion 53-86 (≤ 47 normal range)	14q21 Ataxin-3 (ATXN3)
Spinocerebellar ataxia (SCA4)	Sensory axonal neuropathy Pyramidal signs		16q22.1 Secretory carrier-associated membrane protein 4 (SCA4)
Spinocerebellar ataxia (SCA5)	Early onset, relatively pure cerebellar ataxia with dysarthria Slow progression		11p13 Mutation in <i>SPTBN2</i> gene
Spinocerebellar ataxia (SCA6)	Slowly progressive, pure cerebellar ataxia with dysarthria, nystagmus Occasional mild sensory loss	CAG expansion 20-33 (≤ 18 normal range)	19p13 Altered $\alpha 1A$ subunit of the voltage-dependent calcium channel (CACNA1A)

Spinocerebellar ataxia (SCA7)	Visual loss, retinal degeneration Dysarthria Variable pyramidal sign	CAG expansion 37->300 (4-35 normal range)	3p14.1-p12 Ataxin-7
Spinocerebellar ataxia (SCA8)	Hyperreflexia, spasticity Impaired vibration sense	CTG expansion 100-250 (15-52 normal range)	13q21 KLHL1AS
Spinocerebellar ataxia (SCA10)	Frequent seizures Neuropathy	ATTCT expansion 280->4500 (10-22 normal range)	22q13 Ataxin-10 (ATXN10)
Spinocerebellar ataxia (SCA11)	Rare Slowly progressive mild ataxia		15q14-q21.3 SCA11
Spinocerebellar ataxia (SCA12)	Tremor at onset Late dementia	Noncoding CAG expansion 45-63 (7-31 normal range)	5q31 Serine Threonine Protein phosphatase 2A (PPP2R2B)
Spinocerebellar ataxia (SCA13)	Childhood onset Associated cognitive delay Short stature	--	19q13.3- q14.4 <i>KCNC3</i> gene
Spinocerebellar ataxia (SCA14)	Facial myokymia Eye movement abnormalities	--	19q13.4 Protein kinase C gamma type

	Axial myoclonus, dystonia, vibratory loss Late onset can be pure ataxia		(PRKC)
Spinocerebellar ataxia (SCA15)	Pure ataxia with slow progression	?	3p24.2-3pter
Spinocerebellar ataxia (SCA16)	Pure ataxia, dysarthria Head Tremor	--	3p26.2pter
Spinocerebellar ataxia (SCA17)	Ataxia Pyramidal and extrapyramidal signs Dementia Widespread cerebellar and cerebral atrophy	CAG expansion 63 (25-42 repeats normal range)	6q27 TATA-box binding protein
Spinocerebellar ataxia (SCA18)	Ataxia Sensorimotor neuropathy	--	1p21-q21
Spinocerebellar ataxia (SCA19)	Slowly progressive ataxia Hyporeflexia Cognitive decline Myoclonus tremor	--	7p22-q32
Spinocerebellar ataxia (SCA20)	Dysarthria Dystonia Calcification of dentate nucleus	--	11p13-q11

Spinocerebellar ataxia (SCA21)	Mild ataxia Cognitive delay Extrapyramidal features Hyporeflexia	--	7p21-p15.1
Spinocerebellar ataxia (SCA22)	Gradual onset, slow progression pure ataxia, nystagmus, and dysarthria	--	1p21-q23
Spinocerebellar ataxia (SCA23)	Ataxia of late onset, slow progression Sensory loss Vibration loss	--	20p13-p12.3
Spinocerebellar ataxia (SCA25)	Severe sensory neuropathy Gastrointestinal symptoms	--	2p21-q15
Spinocerebellar ataxia (SCA26)	Dysarthria Ocular pursuit abnormalities	--	19p13.3
Spinocerebellar ataxia (SCA27)	Gait and limb ataxia, tremors Orofacial dyskinesias Behavioral outbursts	Fibroblast Growth Factor 14 related Truncating mutations	13q34
Spinocerebellar ataxia (SCA28)	Ophthalmoparesis Hyperreflexia		18p11.22-q11.2
Spinocerebellar ataxia (SCA29)	Early-onset, nonprogressive ataxia		18p11.22-q11.2

	Vermian hypoplasia		
Spinocerebellar ataxia linked to 16q22	Late-onset ataxia Hearing loss Slowly progressive gait and limb ataxia Nystagmus	Mutation in the puratrophin-1 gene	16q22
Dentatorubropallidoluysian atrophy (DRPLA)	Chorea Seizures Myoclonus Dementia	Triplet repeat expansion leads to altered protein product	12p13.31 Atrophin-1 with toxic gain of function

*Gait ataxia is a constant feature

Recessively Inherited Ataxias With Spinocerebellar Dysfunction

Ataxia with selective vitamin E deficiency

- Gene, inheritance, and pathogenesis: This is a rare autosomal recessive disorder resulting from a mutation that affects the gene for alpha-tocopherol transfer protein.
- Clinical features
 - It is phenotypically similar to Friedreich ataxia (FRDA), with head titubation (28%), SCA, areflexia, and proprioception loss.
 - Skin is affected by xanthelasmata and tendon xanthomas.
 - Onset varies from ages 2-52 years and usually occurs in people younger than 20 years; it slowly progresses over decades.
- Laboratory findings: Measurements include low-to-absent serum vitamin E and high serum cholesterol, triglyceride, and beta-lipoprotein.
- Treatment: Treatment consists of vitamin E supplementation. A dose of 400-1200 IU/d improves neurologic function. This should be maintained for life.

Friedreich ataxia

- Gene, inheritance, and pathogenesis
 - The prototype disorder of familial spinocerebellar degeneration, FRDA was the first identified recessively inherited condition with a mutation involving a triplet repeat expansion. Of patients with FRDA1, 96% are

homozygous for a GAA expansion in intron 1 of the *X25* gene. The number of GAA repeats ranges from 7-38 in normal alleles and from 66 to more than 1700 triplets in disease-causing alleles. The remaining cases are compound heterozygotes for a GAA expansion and a frataxin point mutation. Most affected individuals carry more than 600 repeats. The DNA-based test for FRDA1 evaluates genomic DNA for the presence of a GAA trinucleotide repeat expansion in the *X25* gene. The mutation leads to formation of the abnormal protein termed frataxin. Tissues carrying this mutation appear to be sensitive to oxidative stress. There is locus heterogeneity.

- Great phenotype variation exists among affected individuals, even within the same family; the types have been divided arbitrarily into late-onset FRDA (LOFA), occurring in people aged 25-39 years, and very-late-onset FRDA (VLOFA), occurring in those older than 40 years. Deep tendon reflexes are retained, and progression is very slow, particularly in Arcadians. These variants have been found to have generally shorter GAA expansions (*X25* alleles). Other postulated mechanisms to account for the differences include tissue-specific variability in triplet expansion size secondary to mitotic instability, *cis*-acting sequence alterations, and other genetic or environmental modifiers.
- Clinical features
 - Onset - Variable age of onset when younger than 20 years
 - Neurologic symptoms - Cerebellar ataxia, dysarthria, nystagmus, uncoordinated limb movements, hypoactive knee and ankle deep tendon reflexes, Babinski sign, impaired position sense, and impaired vibratory sense
 - Cardiac findings - Symmetric concentric hypertrophic cardiomyopathy, congestive heart failure, and subaortic stenosis
 - Skeletal findings - Pes cavus, scoliosis, and hammer toes
 - Metabolic abnormalities - Abnormal glucose tolerance test results, diabetes mellitus, and diabetic ketoacidosis
- Laboratory findings
 - Abnormal electrocardiographic findings
 - Abnormal echocardiographic findings
 - Abnormal findings on motor and sensory nerve conduction studies
 - Cerebellar atrophy and a thin spinal cord on MRI
 - Evidence of iron accumulation within mitochondria of FRDA fibroblasts subjected to oxidative stress, resulting in impaired respiratory function
 - DNA mutation analysis
- Treatment^[31]: Treatment protocols currently include coenzyme Q and other antioxidants that are being newly developed (eg, mitoquinone, idebenone).^[32,33] Preliminary trials have shown a favorable effect on the bioenergetics of cardiac and skeletal muscle and slowing of progression of selected aspects in the ataxia rating scale used.

Abetalipoproteinemia

- Gene, inheritance, and pathogenesis: This rare autosomal recessive disorder is characterized by low levels of low-density lipoproteins (LDLs) and very low-density lipoproteins (VLDLs). It features defective assembly and secretion of apolipoprotein B (Apo-B)-containing lipoproteins by the intestines and the liver. Mutations appear to affect the

microsomal triglyceride transfer protein (*MTP*) gene. The heterodimeric protein is responsible for transfer of neutral lipids across cell membranes. MTP may have an added role as a chaperone involved in Apo-B binding.

- Clinical features
 - Areflexia, proprioceptive dysfunction, loss of reflexes, and Babinski sign (prominent findings)
 - By 5-10 years, gait disturbances and cerebellar signs
 - Malabsorptive state in the early years with steatorrhea and abdominal distension
 - Pes cavus and scoliosis present in some patients
 - Pigmentary retinopathy
- Laboratory findings
 - Acanthocytosis on peripheral blood smears (constant finding)
 - Decreased serum cholesterol
 - Increased high-density lipoprotein cholesterol levels
 - Low levels of LDL and VLDL
 - Low triglyceride levels
 - DNA mutation analysis
- Treatment
 - High-dose supplementation of vitamin E has a beneficial effect on neurologic symptoms.
 - Administer other fat-soluble vitamins (ie, D, A, K).

Hypobetalipoproteinemia

Because of the clinical similarity with abetalipoproteinemia, this autosomal dominant disorder is discussed in this section. It is clinically indistinguishable from abetalipoproteinemia, especially in its homozygous form. It is caused by mutations that affect the *APOB* gene, which affects turnover of Apo-B. Neurologic and nonneurologic manifestations are similar in homozygotes. Heterozygotes, on occasion, also may be affected. It is characterized by extremely low plasma levels of Apo-B, as well as low levels of total cholesterol and LDL cholesterol.

Table 5. Recessively Inherited Chronic/Progressive Ataxias with Spinocerebellar Dysfunction

Disorder/Syndrome	Neurologic Phenotype	Inheritance	Gene Locus	Gene Product/Biochemical Defect
Ataxia with selective vitamin E deficiency	Chronic ataxia	Autosomal recessive	8q13.1-q13.3	Mutated alpha-tocopherol transfer protein (ATTP) binds alpha-tocopherol, enhancing its transfer between separate membranes Vitamin E likely has a role

				in preventing modification of lipoproteins by oxidative stress
Friedreich ataxia	Progressive ataxia plus	Autosomal recessive	9q13-q21.1	Expansion of GAA triplet repeats leads to a defective protein frataxin, abnormal mitochondrial function, oxidative stress, and accumulation of iron
Abetalipoproteinemia	Progressive ataxia plus	Autosomal recessive	4q24	MTP catalyzes the transport of triglyceride, cholesteryl ester, and phospholipid between phospholipid surfaces and is also required for the secretion of plasma lipoproteins that contain Apo-B Defects in the transfer protein result in loss of ability to produce Apo-B-containing lipoproteins with secondary malabsorption of vitamin E
Hypobetalipoproteinemia*	Chronic ataxia	Autosomal dominant	2q24	In the homozygous state, affected individuals are indistinguishable from those with abetalipoproteinemia Defective Apo-B, VLDL, and LDL result in hypocholesterolemia

*Listed here due to overlap of clinical features with abetalipoproteinemia.

Recessively Inherited Ataxias Associated With Defective DNA Repair

Many of the disorders discussed involve defects in DNA repair that require a complex sequence of events. In disorders of these pathways, multiple gene defects are involved. These disorders carry a poor outcome because no specific treatments are

available at present. Complementation analysis helps determine if pathogenic mutations are in the same or different genes. Cell fusion of 2 different (diploid) cell lines from affected individuals (eg, from xeroderma pigmentosum) is attempted; DNA repair mechanisms then are studied in the new cell line. If the DNA repair defect is corrected in a tetraploid cell line, the mutations complement, and the 2 cell lines are said to define 2 separate complementation groups.

Cockayne syndrome

- Gene, inheritance, and pathogenesis: Type I (or A) and type II (or B) are the 2 predominant forms. Inheritance is autosomal recessive for both. Defective repair of transcriptionally active DNA is the underlying basis of the disorder. Cultured skin fibroblasts from these patients display abnormal UV sensitivity. Mutations in the excision-repair cross-complementing group 8 gene (*ERCC8*) in type I or the excision-repair cross-complementing group 6 gene (*ERCC6*) in type II result in Cockayne syndrome. Early death in the second or third decade is usual.
- Clinical features
 - Blindness, cataracts, and pigmentary retinopathy
 - No increase in incidence of malignancy in these patients
 - Microcephaly
 - Neurologic features including ataxia, pyramidal and extrapyramidal dysfunction, and seizures
 - Photosensitivity of skin
 - Systemic hypertension, sexual infantilism, renal and hepatic dysfunction
 - Wizenod facies (similar to progeria)
- Laboratory findings
 - Calcification of basal ganglia on CT scanning, and white matter changes on MRI
 - At least 2 complementation groups
 - Disturbed visual and brainstem auditory evoked responses indicative of CNS demyelination
 - Increased cellular sensitivity to UV light
 - Mutation testing in specialized laboratories

Xeroderma pigmentosum

- Gene, inheritance, and pathogenesis
 - This genetically heterogeneous disorder is due to a defect in DNA excision repair following UV exposure.
 - The condition differs from Cockayne syndrome because of the presence of skin tumors, absence of intracranial calcifications, and a different molecular defect. This disorder also has a poor prognosis.
- Clinical features
 - Ataxia, chorea, and axonal polyneuropathy
 - Cutaneous photosensitivity and multiple cancers
 - Mental and motor retardation
 - Microcephaly
 - Sensorineural deafness
- Laboratory findings: Defective DNA repair after ultraviolet radiation damage

Ataxia telangiectasia

This progressive, recessively inherited ataxia manifests in early childhood. It is more common in certain ethnic populations, including in those of Amish, Mennonite, Costa Rican, Polish, British, Italian, Turkish, Iranian, and Israeli descent.

- Gene, inheritance, and pathogenesis: A defective truncated protein that belongs to the phosphatidylinositol-3 kinase family of proteins results from mutations that affect the *ATM* gene locus. This protein phosphorylates key substrates that are involved in DNA repair. The disease begins when patients are aged 1-3 years. No treatment is available other than supportive care and careful management of complications with modified chemotherapy
- Clinical features
 - Choreoathetosis
 - Cutaneous and bulbar telangiectasia (present in teenagers and older individuals)
 - Immunodeficiency and increased susceptibility to infections
 - Oculomotor apraxia
 - Progressive ataxia and slurred speech
 - Susceptibility to cancer (eg, leukemia, lymphoma)
- Laboratory findings
 - Molecular genetic testing is performed for mutations affecting the *ATM* gene locus (11q22.3). For those patients in whom mutations cannot be identified, other supportive laboratory evidence must be sought
 - Elevated (>10 ng/mL) serum alpha-fetoprotein is found in 90-95% of patients.
 - Findings on colony survival assay, ie, colony formation of a lymphoblastoid cell line following irradiation, are abnormal.
 - Karyotyping abnormalities involve 7-14 chromosomal translocation in 5-15% of cells after phytohemagglutinin stimulation of lymphocytes in peripheral blood.
 - Breakpoints result in translocation at the 14q11 and 14q32 sites.

Ataxia telangiectasia–like disorders

This group includes the following disorders: ataxia with oculomotor apraxia type 1 (AOA1), ataxia with oculomotor apraxia type 2 (AOA2), and ARSACS.

- Ataxia with oculomotor apraxia type I
 - Gene, inheritance, and pathogenesis: The disorder begins in childhood, proceeding to loss of ambulation in 7-10 years. The gene locus at 9p13.3 codes for a protein aprataxin. Mutations in this gene are pathogenic. The protein appears to have a role in DNA repair.
 - Clinical features
 - Progressive cerebellar ataxia
 - Oculomotor apraxia progressing to complete ophthalmoplegia
 - Motor neuropathy, progressive distal amyotrophy
 - Normal cognition in Portuguese families, decline in cognition noted in Japanese families

- Laboratory findings
 - Hypoalbuminemia
 - No specific diagnostic tests available
- Ataxia with oculomotor apraxia type 2
 - Gene, inheritance, and pathogenesis: The disorder begins in the second decade of life. The gene locus is 9q34, and the gene product is called senataxin. The protein is thought to function as a helicase involved in various aspects of DNA transcription and repair, RNA maturation, and termination.
 - Clinical features
 - Axonal sensorimotor neuropathy
 - Oculomotor apraxia is an inconsistent feature.
 - Laboratory findings
 - Cerebellar atrophy on imaging
 - Elevated alpha-fetoprotein

Table 6. Recessively Inherited Chronic/Progressive Ataxias Associated with DNA Repair Defects

Disorder/Syndrome	Neurologic Phenotype	Inheritance	Gene Locus	Gene Product/Biochemical Defect
Cockayne syndrome type A	Progressive ataxia plus Early onset severe syndrome	Autosomal recessive	5q11	<i>ERCC8</i>
Cockayne syndrome type B	Progressive ataxia plus Classical type	Autosomal dominant	10q11-q21	<i>ERCC6</i>
Xeroderma pigmentosum	Progressive ataxia plus	Autosomal recessive	Genetically heterogeneous with several complementation groups identified 9q34 locus (A) Other complementation groups involved are 2q21 (B & CS); 3p25.1 (C); 19q13.2(D);	Mutations result in either defective damage-specific DNA-binding protein or defective excision repair (<i>ERCC</i>) Neurologic manifestations beginning in childhood relate to complementation group

			Unknown (E); 16p13 (F); 13q32-33 (G & CS)	
Ataxia Telangiectasia	Progressive ataxia plus	Autosomal recessive	11q22-q23	<i>ATM</i> gene Product belongs to the P-13 kinase family of proteins involved in DNA damage recognition
Ataxia with oculomotor apraxia type 1 (AOA1)	FRDA-like hypoalbuminemia	Autosomal recessive	9p13.3	Aprataxin (APTX) Role in single- stranded DNA repair
Ataxia with oculomotor apraxia type 2 (AOA2) Changed to autosomal recessive cerebellar ataxia (SCAR1)	Ocular apraxia is an inconsistent feature. Ataxia Distal amyotrophy Peripheral neuropathy	Autosomal recessive	9q34	Senataxin (SETX) Protein involved in RNA maturation and termination

Recessively Inherited Ataxias Associated With Protein Translation/Folding Defects

Spastic ataxia of Charlevoix-Saguenay

- Gene, inheritance, and pathogenesis
 - ARSACS is an autosomal recessive spastic ataxia of Charlevoix-Saguenay region. This is an early-onset ataxia, manifesting in infancy or early childhood, with a high prevalence in the Charlevoix-Saguenay region of northeastern Quebec.
 - The estimated carrier frequency in Charlevoix-Saguenay region is 1/22. It has also been described in other regions of the world such as Mediterranean areas and Japan. Mutations in the *SACS/IN* gene encode a protein saccin that is believed to function as a chaperone involved in protein folding.
- Clinical features

- Progressive ataxia with pyramidal, cerebellar, and distal neuropathy sensorimotor neuropathy
- Nystagmus
- Slurred speech
- Hypermyelinated retinal nerve fibers leading to retinal striations
- Skeletal abnormalities, including swan neck–like deformities of the fingers, pes cavus, and hammer toes
- Laboratory findings
 - Decreased sensory nerve conduction velocities (NCV)
 - Decreased motor NCV
 - Loss of large myelinated fibers on nerve biopsy

Leukoencephalopathy with vanishing white matter (van der Knaap syndrome)^[34,35]

- Gene, inheritance, and pathogenesis
 - Leukoencephalopathy with vanishing white matter (VWM) has an autosomal recessive inheritance with an age-dependent penetrance.
 - The gene is located on band 3q27.^[36] The mutation involves a gene that codes for the eukaryotic translation initiation factor (eIF2B). The gene likely controls regulation of translation under conditions of stress. No effective treatment is known to halt progression of the disorder, although symptomatic and supportive measures can improve the quality of life.
- Clinical features
 - Cerebellar ataxia and spasticity are prominent.
 - Chronic progressive neurologic deterioration and episodic exacerbation follow in late infancy or early childhood.
 - Episodes of deterioration follow minor infection and head trauma, leading to periods of lethargy or coma.
 - Cognitive ability may show decline but is relatively preserved compared to the severity of motor deficit.
 - Initial motor and mental development is normal or mildly delayed.
 - Optic atrophy and epilepsy may be additional features.
- Laboratory findings
 - Cerebellar atrophy varies from mild to severe and primarily involves the vermis.
 - Elevated CSF glycine is a marker for this disorder.
 - MRI indicates symmetric involvement of the cerebral hemispheric white matter, which acquires a signal intensity close to or the same as CSF on proton density, T2-weighted, T1-weighted, and fluid-attenuated inversion recovery images.
 - Magnetic resonance spectroscopy shows a significant decrease to near absence of normal signals from the white matter, except for lactate and glucose (the signals of which become more prominent with disappearance of other normal signals). Signals over the cortex remain relatively normal.
 - Pathologic studies confirm white matter rarefaction and loss of myelinated white fibers. Microcystic changes are reported in the periventricular white matter.

4H syndrome

- 4H syndrome is a recessively inherited phenotype with distinctive clinical features and a hypomyelinating leukodystrophy. To date, no gene locus or mutations have been identified.
- Clinical features
 - Early onset progressive ataxia
 - Short stature
 - Hypodontia
 - Delayed puberty secondary to gonadal dysfunction
- Laboratory
 - MRI shows white matter signal abnormalities consistent with central hypomyelination and cerebellar atrophy.
 - Sural nerve biopsy shows debris-lined myelin clefts, vacuolar disruption, and loss of normal myelin periodicity.

Table 7. Recessively Inherited Chronic/Progressive Ataxias Associated with Protein Translation and Folding Defects

Disorder/Syndrome	Neurologic Phenotype	Inheritance	Gene Locus	Gene Product/Biochemical Defect
Autosomal recessive spastic ataxia of Charlevoix-Saguenay	Chronic ataxia Spasticity Retinal abnormalities	Autosomal recessive	13q11	SACS gene codes for saccin, which is involved in chaperone-mediated protein folding
Leukoencephalopathy with VWM	Progressive ataxia Spasticity Optic atrophy Seizures	Autosomal recessive	3q27	Mutations affect eIF2B
4H syndrome	Short stature Slowly progressive ataxia Hypogonadism Hypomyelination	Autosomal recessive	Not known	Not known

Recessively Inherited Chronic/Progressive Ataxias Associated With Inherited Enzymatic Defects

Refsum disease

- Gene, inheritance, and pathogenesis: This autosomal recessive disorder is associated with impaired oxidation of phytanic acid. Elevated phytanic acid levels in the nervous system are associated with neurotoxicity.
- Clinical features
 - Onset in the second to third decade of life
 - Cerebellar ataxia (may be superimposed in some patients)
 - Early presentation of night blindness and pigmentary degeneration of the retina
 - Polyneuropathy with elevated CSF protein
 - Sensorineural deafness
 - Skin (ichthyosis) and cardiac (arrhythmia) abnormalities
- Laboratory findings
 - Cultured fibroblasts show reduced ability to oxidize phytanic acid.
 - Elevated phytanic acid levels in the plasma and urine are diagnostic.
- Treatment: Refsum disease has a relapsing-remitting course. Drastic reduction in dietary phytanic acid (supplemented by plasmapheresis) at onset can ameliorate the neuropathy and possibly other clinical abnormalities.

Cerebrotendinous xanthomatosis

- Gene, inheritance, and pathogenesis: This autosomal recessive disorder is caused by a defect in bile acid synthesis. Cholestanol accumulates in the tissues, including the nervous system. The defect is due to deficiency of hepatic sterol 27-hydroxylase, a mitochondrial enzyme.
- Clinical features
 - Palatal myoclonus and seizures
 - Peripheral neuropathy
 - Progressive ataxia with mental decline
 - Pseudobulbar palsy
 - Tendon xanthomas
 - Cataracts
- Laboratory findings
 - Elevated cholestanol and Apo-B in CSF
 - Low plasma cholesterol; elevated plasma cholestanol

- Low-to-absent chenodeoxycholic acid in the bile
- Treatment: Lifelong oral administration of chenodeoxycholic acid (750 mg/d) is effective if initiated early. A 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor also can be added to inhibit cholesterol biosynthesis.

Biotinidase deficiency

- Gene, inheritance, and pathogenesis: Because of the lack of free biotin, biotinidase deficiency results in dysfunction of 3 mitochondrial carboxylases. It is recessively inherited, and the underlying defect involves mutations of the 3p25 locus for biotinidase.
- Clinical features
 - Delayed presentation (second year of life)
 - Intermittent ataxia, sensorineural hearing loss
 - Myoclonic seizures, developmental delay
 - Skin rashes, alopecia
- Laboratory findings
 - Organic aciduria (eg, elevated beta-hydroxyisovalerate, lactate, beta-methylcrotonylglycine, beta-hydroxypropionate, methylcitrate)
 - Mild hyperammonemia
 - Diffuse cerebral and cerebellar atrophy on cranial MRI
 - Metabolic acidosis, lactic acidosis
 - Biotinidase activity in serum and fibroblasts
 - Mutation analysis
- Treatment
 - Biotin 5-20 mg/d PO is remarkably effective in reversing neurologic and cutaneous symptoms.
 - Hearing and visual dysfunction may be resistant to treatment.

L-2-hydroxyglutaricaciduria

- Gene, inheritance, and pathogenesis: This autosomal recessive inherited defect is characterized by excessive excretion of L-2-hydroxyglutaric acid in the urine. The precise molecular basis is not well established. The clinical course is of slowly progressive neurodegenerative disorder.
- Clinical features
 - Age of onset from 6-20 years
 - Presence of cognitive delay and epileptic seizures
 - Progressive ataxia, dysarthria, and extrapyramidal dysfunction
 - Added features of short stature and macrocrania
- Laboratory findings
 - Elevated 2-hydroxyglutaric acid in plasma, urine, and CSF
 - Elevated lysine in plasma and CSF

- Highly specific MRI pattern showing subcortical leukoencephalopathy with bilateral high signal intensity in dentate nuclei and putaminal regions

Succinic-semialdehyde dehydrogenase deficiency^[37]

- Gene, inheritance, and pathogenesis: Succinic-semialdehyde dehydrogenase deficiency (SSADH) is a recessively inherited disorder affecting the gamma-aminobutyric acid (GABA) degradation pathway. Although it is characterized by excretion of large amounts of 4-hydroxybutyric acid in the urine, phenotype varies widely.
- Clinical features
 - Ataxia
 - Hypotonia
 - Nonspecific neurologic features such as cerebral palsy and developmental delay
 - Psychomotor retardation, language delay
- Laboratory findings
 - Elevated 4-hydroxybutyric acid in plasma, urine, and CSF
 - High free GABA in CSF
 - Cerebellar atrophy on MRI
- Treatment
 - L-carnitine supplementation has been tried with improvement in muscle tone.
 - Vigabatrin, an inhibitor of GABA transaminase, has proven effective in low doses of 25 mg/kg/d.

Late-onset sphingolipidoses

These complex biochemical defects are related to specific deficiencies of lysosomal enzymes (see Table 8 below). The brain and other tissues such as the liver store abnormal sphingolipids. The presentation is a combination of cognitive deterioration, seizures, and gait abnormalities due to a combination of pyramidal features (spasticity), cerebellar dysfunction (ataxia), extrapyramidal features (eg, dystonia), choreoathetosis, and ophthalmologic abnormalities. Ataxia almost never is the sole clinical symptom. Other systemic features can include coarse facies, organomegaly, and dysostosis multiplex. Because these disorders are progressive, symptoms and signs can be seen in combination. The disorders are autosomal recessive. Skin fibroblast examination under electron microscope is an effective screening tool. Definitive diagnosis can be established by lysosomal enzyme assay in leukocytes or cultured skin fibroblasts.

Congenital disorders of glycosylation

The congenital disorders of glycosylation (CDG) represent a new class of disorders that result from abnormalities of carbohydrate-deficient glycoproteins, particularly transferrin. The disorder has been reported from Scandinavian countries as well as other European countries. Most are autosomal recessive conditions; several (nearly 20 at the latest count) clinical and biochemical types have been characterized. Because glycoproteins are important constituents of the developing brain, CNS involvement and multisystem manifestations are frequent.

- Gene, inheritance, and pathogenesis: CDG type 1a is caused by mutations affecting the enzyme phosphomannomutase; the gene locus is located on sub band 16p13.3. The enzyme is involved in the N-glycosylation pathway. Several other disorders involving the O-glycosylation pathway have now been recognized; the Walker-Warburg syndrome and the muscle-eye-brain disease are examples. For the purposes of the present discussion on ataxia the authors restrict discussion to CDG type 1a. The mortality rate is approximately 20% in the first 2 years. Only supportive treatment is available.
- Clinical features
 - Stage of ataxia; mental deficiency during infantile and childhood stage
 - Delayed development, failure to thrive, hypotonia, and multisystem organ failure
 - Dysmorphic facial features, including prominent ears and nose
 - Fat pads over buttocks, abnormal patches of skin over thighs (orange peel skin), and inverted nipples (considered characteristic clinical features)
 - In the teenage years, evident lower limb atrophy and peripheral neuropathy
 - Severe mental retardation and hypogonadism recognized in later years
- Laboratory findings
 - Decreased serum glycoproteins
 - MRI showing striking pontocerebellar atrophy
 - Reduced thyroxine-binding globulin levels
 - Sialic acid, galactose, and *N*-acetylglucosamine deficiency in total serum glycoproteins
 - Synthesized proteins with fewer attached carbohydrate moieties than normal glycoproteins
 - Separation of proteins based on charge when an electric field is applied to serum
 - Sialotransferrins, a specific class of glycoproteins, behave differently in serum from patients with CDG than in serum from individuals without CDG; patients with CDG have less sialic acid, a negatively charged sugar.
 - The pattern of separation during electrophoresis (transferrin isoimmunoelectrophoresis) is considered diagnostic for this disorder.
 - Phosphomannomutase deficiency in leukocytes, fibroblasts, or liver
 - Consideration of molecular analysis of phosphomannomutase 2 gene (*PMM2*) in some subtypes

Marinesco-Sjögren syndrome

- Gene, inheritance, and pathogenesis: Marinesco-Sjögren syndrome (MSS) is an autosomal recessive disorder. MSS is mapped to chromosome arm 5q31, but genetic heterogeneity is evident. In some families, mutations have been identified in the gene *SIL1*^[38], which encodes a nucleotide exchange factor for the heat-shock protein 70 (HSP70) chaperone HSPA5. The disorder is now thought to be a consequence of dysfunction of the endoplasmic reticulum and disturbed SIL1-HSPA5 interaction and protein folding. This disorder has overlapping features with lysosomal disorders. Ophthalmologic, skeletal, and gonadal abnormalities are frequently seen.
- Clinical features
 - Microcephaly
 - Cataracts

- Cerebellar ataxia
- Mild-to-moderate mental retardation
- Neuromuscular weakness
- Short stature
- Hypergonadotropic hypogonadism
- Skeletal anomalies of kyphosis, scoliosis, and coxa valga
- Laboratory findings
 - Massive cerebellar cortical atrophy on imaging
 - Elevated serum creatine kinase
 - Myopathic changes on muscle biopsy and numerous enlarged lysosomes containing whorled lamellar or amorphous inclusion bodies by electron microscopy

Table 8. Recessively Inherited Chronic/Progressive Ataxias Associated with Inherited Enzyme Defects

Disorder/Syndrome	Neurologic Phenotype	Inheritance	Gene Locus	Gene Product/Biochemical Defect
Refsum disease	Progressive ataxia plus	Autosomal recessive	10pter-p11.2	Mutations affecting the gene coding for phytanoyl-CoA hydroxylase
Cerebrotendinous xanthomatosis	Chronic progressive ataxia	Autosomal recessive	2q3-qter	Defective mitochondrial cytochrome-P450 sterol27-hydroxylase CYP-27A1 leading to accumulation of plasma cholestanol
Biotinidase deficiency	Progressive ataxia plus	Autosomal recessive	3q25	Deletions resulting in multiple carboxylase deficiency and impaired release of biotin from biocytin, the product of biotin-dependent carboxylase degradation
L-2 hydroxyglutaric acidemia	Chronic progressive ataxia	Autosomal recessive	Unknown locus	Deficiency of hepatic hydroxyglutaric acid dehydrogenase
Succinic-semialdehyde dehydrogenase deficiency	Progressive ataxia plus	Autosomal recessive	6p22	Deficiency of succinic semialdehyde dehydrogenase Accumulation of 4-

				hydroxybutyric acid in plasma and urine
Late infantile and juvenile sphingolipidoses	Progressive ataxia plus	Autosomal recessive	1. 22q13.3-qter/ 2. 14q31 3. 1q21 18q11-q12 4. 15q23-q24	1. Deficiency of arylsulfatase A/sphingolipid activator Protein (SAP) 2. Deficiency of galactosylceramide beta-galactosidase 3. Deficiency of beta-glucocerebrosidase 4. Abnormal uptake of cholesterol and defective esterification leading abnormal cholesterol ester storage 5. Defect in hexoaminidase A or of the GM2 protein activator
1. Metachromatic leukodystrophy 2. Krabbe globoid cell leukodystrophy 3. Gaucher type III 4. Niemann-Pick C disease 5. GM2 gangliosidosis	Seizures Psychomotor regression Spasticity Extrapyramidal features Supranuclear gaze palsies			
Congenital disorders of glycosylation type Ia	Progressive ataxia plus	Autosomal recessive	16p13.3-p13.2	Mutations in the gene encoding for phosphomannomutase
Marinesco-Sjögren syndrome	Chronic ataxia Cataract Hypotonia Myopathy	Autosomal recessive	5q31	Disturbed SIL1 and HSP70 chaperone HSPA5 protein folding interaction

Recessively Inherited Ataxias Associated With Mitochondrial Cytopathies

Neuropathy, ataxia, retinitis pigmentosa, and peripheral neuropathy syndrome (maternal inheritance)

Gene, inheritance, and pathogenesis: Neuropathy, ataxia, retinitis pigmentosa, and peripheral neuropathy (NARP) syndrome is a mitochondrial disorder that displays maternal inheritance. Affected individuals present with features of cerebellar ataxia, seizures, cognitive impairment, and peripheral neuropathy. The condition carries a variable phenotype and also may occur sporadically. The underlying defect involves a mitochondrial adenosine triphosphate (ATP) synthase gene (subunit 6) affecting nucleotide 8993, mutations of which also can result in the Leigh syndrome phenotype. The diagnosis can be confirmed by mitochondrial DNA mutation analysis.

Leigh disease

- Gene, inheritance, and pathogenesis: This disorder has distinct neuropathologic findings, highly variable clinical presentation, and can be caused by multiple biochemical and molecular genetic defects. Autosomal recessive inheritance and maternal inheritance (mutations in mitochondrial DNA) patterns exist.
- Clinical features: Clinical features include protean manifestations due to multifocal lesions in the brainstem, thalamus, and cerebellum; the most important of these are as follows:
 - Oculomotor - Nuclear or supranuclear ophthalmoplegia, central nystagmus with rotary and horizontal components
 - Course - Relapsing-remitting course, rarely progressively fatal
 - Respiratory - Characterized by unexplained hyperventilation, apnea, and irregular respiration (air hunger)
 - Neurologic - Truncal ataxia, incoordination, and intention tremor evident as child begins to walk
- Laboratory findings
 - Characteristic symmetric lesions can be demonstrated in the thalamus, putamen, and globus pallidus on T2-weighted MRI sequences. The lesions also are distributed in the brainstem and cerebellum.
 - Lactate and pyruvate are elevated in the CSF.
 - Perform enzyme function assays on cultured fibroblasts, muscle, or liver tissue. Frequently, more than one of these tissues should be assayed because of the lack of correlation between enzyme activities in muscle and skin.
 - Hyperammonemia, hypoglycemia, and organic aciduria are not present.
 - Multiple mitochondrial enzymes have been demonstrated to be affected in this disorder, particularly the pyruvate dehydrogenase (PDH) complex, cytochrome c oxidase, and the mitochondrial adenosine triphosphatase (ATPase) 6 gene.
 - Neuropathologic lesions show incomplete necrosis and spongiform changes in the neuropil with relative preservation of the neurons, resulting in a spongiosis. Vascular proliferation also occurs, and white matter changes can be seen.
- Treatment: No treatment is known to actually benefit patients. Vitamin B1 (thiamine) supplementation has been administered without documented benefit. Recently, the ketogenic diet has been reported to be useful in treating patients with PDH complex deficiency.

Coenzyme-Q10-associated ataxia

CoQ-10 is involved in facilitation of electron transfer between the various dehydrogenases and cytochromes participating in the respiratory chain and oxidative phosphorylation reaction. Ubiquinone deficiency presents with many different clinical phenotypes ranging from myopathy to Leigh's disease.

- Gene inheritance and pathogenesis: Autosomal recessive, genetic heterogeneity is likely. Mutations (missense) in the *CABC1* gene, also called COQ8 or ADCK3, coding for a putative protein kinase in the ubiquinone biosynthesis pathway have recently been shown to be associated with this form of CoQ-10 deficiency.^[39]
- Clinical features

- More than 20 patients have been described with a recessively inherited form of muscle CoQ-10 deficiency who present with a slowly progressive ataxia in childhood, associated with cerebellar atrophy.^[40]
- Associated features include developmental delay, mental retardation, and seizures.
- Laboratory
 - A few patients demonstrate elevations in plasma lactate.
 - Decreased CoQ concentration in muscle or fibroblasts.
- Treatment
 - Response to CoQ-10 supplementation is excellent in some patients.^[40]

Table 9. Recessively Inherited Chronic/Progressive Ataxias Associated with Mitochondrial Cytopathies

Disorder/Syndrome	Neurologic Phenotype	Inheritance	Gene Product/Biochemical Defect
NARP syndrome	Progressive ataxia plus	Maternal inheritance	Mitochondrial ATP 6 NARP 8993 mutation causing base substitution T-G or T-C at nucleotide position 8993
Leigh disease	Progressive ataxia plus Lactic acidosis	Autosomal recessive/maternal inheritance	Multiple biochemical and molecular defects underlie the condition, eg, PDHC deficiency, cytochrome oxidase C deficiency, mitochondrial ATPase 6
CoQ-10 responsive ataxia	Progressive ataxia in childhood Developmental delay Seizures Cerebellar atrophy on MRI	Autosomal recessive	Mutations in the gene <i>CABC1</i> or <i>ADCK3</i> are described. The gene codes for a putative protein kinase associated with ubiquinone biosynthesis.

Progressive Ataxias With Polymyoclonus and Epileptic Seizures

The progressive myoclonic epilepsies (PMEs) constitute a group of seizure disorders with phenotypic features of myoclonic and other generalized seizures, ataxia, and cognitive defects. These features occur in variable combinations that progress over time. These disorders are often difficult to distinguish on purely clinical grounds.

Dodecamer Repeat Expansions

Unverricht-Lundborg disease

- Gene, inheritance, and pathogenesis: PME of the Unverricht-Lundborg type (EPM1) is autosomal recessive with an approximate age of onset of 10 years. EPM1 mostly has been reported in a genetically homogeneous population, permitting studies using linkage disequilibrium to narrow the gene defect to a small region of sub-band 21q22.3. The gene *CST6* codes for a protein called cystatin B, a noncaspase cysteine protease inhibitor. Cystatin B mRNA is reduced markedly in patients with EPM1. The mutation results from an unstable dodecamer repeat expansion in the promoter region of the *CST6* gene.
- Clinical features
 - Ataxia developing late in the disease course
 - Mild mental deterioration
 - Progressive disability from stimulus-sensitive myoclonus and generalized tonic-clonic (GTC) seizures
- Laboratory findings
 - EEG findings are nonspecific, showing background slowing and paroxysmal bursts of generalized spike-wave abnormalities.
 - Giant somatosensory evoked potentials can be elicited.
- Treatment
 - *N*-acetylcysteine has been found effective in an open trial in 4 patients. A marked decrease in myoclonus and some normalization of somatosensory evoked potentials with *N*-acetylcysteine treatment has been documented.
 - Phenytoin aggravates symptoms.
 - Piracetam has been useful in the treatment of myoclonus.

Inherited Enzyme Defects

Lafora body disease

- Gene, inheritance, and pathogenesis: PME of the Lafora type (EPM2/MELF) resembles EPM1 clinically. EPM2 is linked to 6q24, where the gene *EPM2A* encodes a protein tyrosine phosphatase termed laforin. Phosphatases are involved in many aspects of neuronal function, including glycogen metabolism and regulation of ionic channels and synaptic transmission. The disorder is fatal. Symptomatic treatment for seizures and myoclonus may be tried.
- Clinical features
 - Ataxia
 - Progressively worsening myoclonic and occipital seizures with visual signs
 - Presentation in late childhood or adolescence, leading to a fatal outcome within a decade

- Laboratory findings
 - MRI shows cerebellar atrophy.
 - Periodic acid-Schiff–positive cytoplasmic inclusion bodies are found in the brain, muscle, liver, and skin. These findings are considered diagnostic.

Neuronal ceroid lipofuscinosis

- Gene, inheritance, and pathogenesis: Neuronal ceroid lipofuscinosis (NCL) describes autosomal recessive disorders in which characteristic storage material is identified within neurons, resulting in their degeneration. NCLs are a group of progressive neurodegenerative disorders that share several clinical features, particularly the presence of seizures and progressive dementia. Several genetically distinct subgroups have been determined based on age at presentation. Each subgroup has a characteristic ultrastructural appearance of the intracellular lipopigment. The gene for the classic late infantile form (*LINCL CLN2*) maps to band 11p15. Mutations in the gene encoding a pepstatin-insensitive lysosomal peptidase have been identified in patients with CLN2, and assays demonstrate that this enzyme is deficient in CLN2 autopsy specimens. The disorders are progressive and fatal. Symptomatic treatment and supportive measures may help improve the quality of life.
- Clinical features
 - Ataxia
 - Dementia
 - Myoclonic seizures, atypical absence seizures, GTC seizures, other seizure types
 - Visual impairment
- Laboratory findings
 - CT scanning and MRI show predominantly cerebellar atrophy. See Media file 3.



Magnetic resonance imaging study of the brain in a patient with neuronal ceroid lipofuscinosis showing cerebellar atrophy on sagittal view.

- Electron microscopic examination of skin or conjunctival biopsy shows typical intralysosomal curvilinear inclusions.
- Giant visual evoked potentials and large somatosensory visual evoked potentials can be elicited.
- Driving responses on the EEG to photic stimulation are abnormal (ie, high-amplitude spike at low rates of stimulation).
- Lysosomal palmitoyl protein thioesterase and tripeptidyl peptidase 1 enzyme analysis may be performed.
- DNA may be examined for mutation analysis.

Mitochondrial Cytopathies

Myoclonic epilepsy with ragged red fibers

- Gene, inheritance, and pathogenesis: MERRF is the prototype disorder in which epilepsy results from deficient mitochondrial energy production. An A-to-G transition mutation at nucleotide pair 8344 in human mitochondrial DNA has been identified in most patients. The mutation creates a specific restriction site on the tRNA^{Lys} gene, producing defects in complex I and IV enzymes of the oxidative phosphorylation system. Myriad cell functions are involved in the control of excitability and are energy dependent. Thus, deficient energy production or utilization can lead to neurologic dysfunction in a variety of ways.
- Clinical features
 - Ataxia
 - Impaired deep sensations (similar to FRDA)
 - Myopathy
 - Sensorineural deafness
 - Short stature
 - Myoclonic and GTC seizures that are often photosensitive and exaggerated by voluntary movements
- Laboratory findings
 - CT scanning may show basal ganglia calcification.
 - Ragged red fibers in muscle biopsy specimens result from the subsarcolemmal aggregation of mitochondria.
 - EEG shows paroxysmal irregular generalized spike-wave complexes with background abnormalities.
 - Lactic acidosis may be present.
 - The pathogenic mutation may be undetectable in leukocytes and may only be detected in other tissues, such as cultured skin fibroblasts, urinary sediment, oral mucosa (from mouthwash), hair follicles, or most reliably, skeletal muscle.
- Treatment
 - The seizure disorder can be treated with conventional anticonvulsant therapy.

- o No treatment for the genetic defect is currently available. Coenzyme Q10 and L-carnitine have been proposed to stabilize mitochondrial dysfunction.

Table 10. Progressive Ataxias with Myoclonus and Epileptic Seizures

Type	Unverricht-Lundborg syndrome	Neurologic Phenotype	Inheritance	Locus	Gene Product/Biochemical Defect
Dodecamer repeat expansion	Unverricht-Lundborg syndrome	Myoclonus Ataxia Seizures	Autosomal recessive	21q22.2	Dodecamer repeat expansions affects gene for cystatin B
Inherited enzyme defect	Lafora body disease	Myoclonus Ataxia Seizures	Autosomal recessive	6q24	Mutation affects a gene encoding for a protein tyrosine phosphatase (laforin) that may disrupt glycogen metabolism
Inherited enzyme defect	Late infantile neuronal ceroid lipofuscinosis	Myoclonus Ataxia Seizures	Autosomal recessive	11p15.5	Gene codes for a lysosomal pepstatin insensitive protease
Mitochondrial cytopathy	MERRF	Myoclonus Ataxia	Maternal inheritance	N/A	mt-DNA mutations affecting tRNA ^{Lys} Defective oxidative phosphorylation

Other Disorders

Angelman syndrome

- Gene, inheritance, and pathogenesis: This is a disorder caused by abnormalities of imprinting. It manifests with significant gait abnormalities and ataxia with characteristic pattern, identified earlier as happy puppet syndrome (this term is no longer used). A number of different pathogenetic mechanisms such as loss of maternal allele, paternal uniparental disomy, mutation of the ubiquitin protein ligase E3A gene (*UBE3A*) account for different subsets of Angelman syndrome.

- Clinical features
 - Microcephaly
 - Prognathia
 - Hypopigmentation of the skin
 - Significant seizures
 - Happy disposition and paroxysmal laughter
 - Poor speech
 - Severe mental retardation
 - Ataxia with jerky arm movements and hyperreflexia
 - Characteristic arm position with wrist and elbow flexion
- Laboratory findings
 - DNA methylation abnormalities in the 15q11-13 region
 - Deletions in 15q11-13 region using fluorescent in situ hybridization (FISH)
 - Uniparental disomy studies
 - *UBE3A* mutation on DNA analysis
 - Mild cortical atrophy on CT scanning or MRI
 - EEG abnormalities that are considered as highly characteristic

Fragile X syndrome/ataxia

- Gene, inheritance, and pathogenesis: Carriers of premutation alleles (55-200 CGG repeats) of fragile X mental retardation 1 (FMR1) are now being identified with one (or more) distinct clinical disorders, including mild cognitive delay and/or behavioral deficits on the fragile X spectrum and a neurodegenerative disorder among older adult carriers. This is known as the fragile X-associated tremor/ataxia syndrome (FXTAS). Awareness of these clinical presentations is important for physicians involved in the care of patients with fragile X syndrome but also more broadly for neurologists caring for adults with tremor, gait ataxia, and parkinsonism. Female carriers of the FMR1 premutation who present with symptoms of tremor and ataxia do not develop features of dementia, unlike males with FXTAS. This protective effect in female carriers remains unexplained at present.
- In the fragile X tremor ataxia syndrome, up to 40% of males and 4-8% of females carrying the premutation can be symptomatic. In the premutation states, the degree of FMR protein (FMRP) amounts are not decreased. The levels may be near normal; however, the amount of mRNA expression is noted to be 8-10 times elevated. This is not seen with the full mutation. The tremor ataxia syndrome is thought to be related to mRNA accumulation and resultant toxicity.

Approach to Patients With a Suspected Inherited Ataxia

The assessment of such a patient involves obtaining a detailed clinical history complemented by an appropriate neurologic examination that delineates the following information:

- Age of onset
- Mode of onset (ie, acute, subacute, chronic)

- Sex
- Natural history (ie, nonprogressive/static, episodic, progressive)
- Associated symptoms/signs that provide localizing information
 - Presence of dystonia or chorea suggesting involvement of the striatum
 - Proprioceptive dysfunction suggesting involvement of spinocerebellar pathways
 - Visual deficits (retinitis pigmentosa), auditory involvement (Refsum disease)
 - Cognitive dysfunction possible early and/or late
- Other systemic features
 - Dysmorphic features and associated congenital malformation may suggest a specific association or clinical syndrome.
 - Cardiac (Friedreich ataxia), renal (NPCA), and cutaneous (xeroderma pigmentosa) features are examples.
- Family history and pedigree analysis provides diagnostic clues and information on possible patterns of inheritance, which are useful for planning investigations and genetic counseling.

Once a specific clinical phenotype is delineated, the investigative process can be initiated based on the clinical features. The initial step involves obtaining specific neuroimaging studies; MRI is often preferable because it can provide detailed information helpful in anatomic localization (ie, signal changes in the cortex, white matter, cerebellum, striatum, and brainstem), and patterns of involvement in some conditions can be diagnostic. In mitochondrial cytopathies, magnetic resonance (MR) spectroscopy (ProtonMRS) can demonstrate an elevated lactate peak and can complement the findings on MRI. A karyotype (demonstrating deletions, duplications, and chromosomal rearrangements), specialized cytogenetic studies (as in Angelman syndrome), and DNA-based molecular diagnostics (as in SCAs, fragile X syndrome, and Angelman syndrome) can be utilized to provide rapid turnaround times for diagnosis.

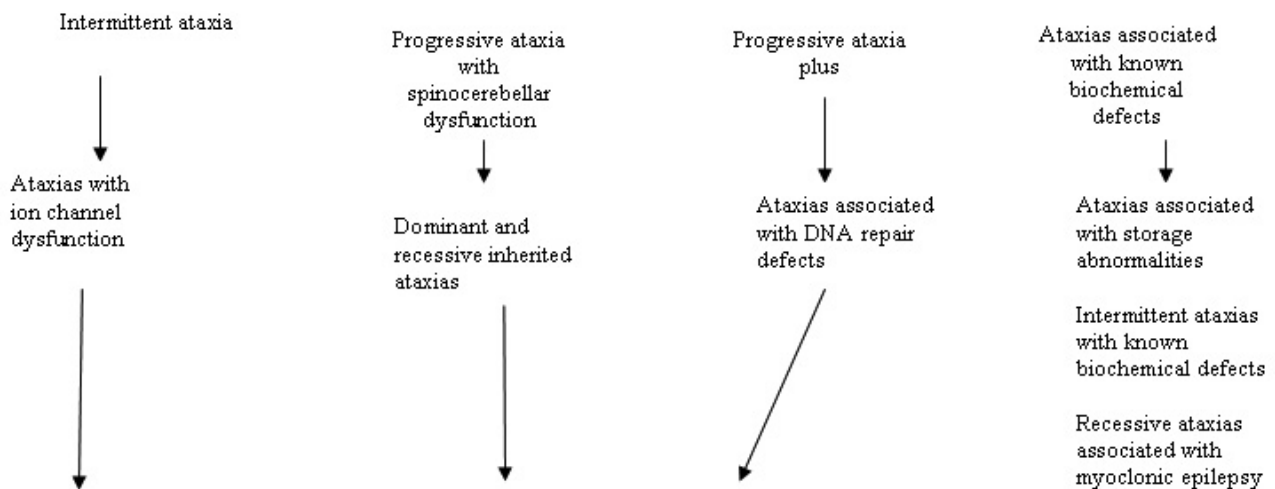
Metabolic screening involves tests such as quantitative studies for plasma lactate, ammonia, carnitine levels, amino acids in blood and urine, urine analysis for organic acid and acylglycines (stable isotope dilution gas chromatography–mass spectrometry [GC/MS]), plasma acylcarnitines (tandem mass spectrometry [MS/MS]), and assays for sialotransferrins (isoelectric focusing of serum transferrins) should be used selectively after consultation with a metabolic geneticist. A schematic approach is suggested (see Media file 2).

Approach to the Evaluation of Inherited Ataxias

Clinical presentation

1. Age of onset
2. Symptoms (episodic, progressive ataxia plus other neurologic features)
3. Progression
4. Family history

Imaging studies such as CT scanning and MRI of the head are of specific value in visualizing the cerebellum and its connections in the brain



In a majority of the conditions described in the text, for which specific information on a mutation is available, mutation-specific targeted screening or sequence analysis of the entire coding region is offered through molecular genetics laboratories across the world. Specific information on the tests and the laboratories is available at <http://www.genetests.org>

*Specific testing:
Isoelectric focusing of sialotransferrins
Skin and muscle biopsy
Electromyography studies on skin
Specific enzyme assays on serum, leukocytes, and cultured fibroblasts for lysosomal storage disorders

Tests listed below can be selected based on the clinical phenotype and may also be used as screening tests for biochemical analytes:
Smears for acanthocytes, vacuolated lymphocytes
Acid-base studies
Blood gas study
Serum uric acid level
Plasma ammonia level
Plasma lactate level
Amino acid screening in plasma, urine and cerebrospinal fluid
Urine organic acid profile
Biotinidase level
Liver function testing
Plasma cholesterol, triglyceride, and lipoprotein electrophoresis

*These test are not necessary in every patient, but more targeted screening based on presentation is recommended

Approach to the biochemical evaluation of inherited ataxia. Screening tests should be targeted to clinical presentations.

Conclusions

With the recent completion of the Human Genome Project, newer gene discoveries have ushered in an era where making diagnoses is not limited to clinical aspects but also relies on establishing a molecular basis. The identification of gene-protein links to specific cellular pathways will add to the understanding and eventually guide the way for future therapeutic advances. When approaching the child or adult with ataxia, the differential diagnosis always must include biochemical defects. The age of onset, mode of presentation, family history, and presence or absence of other neurologic signs are involved heavily in determining the screening and specific tests used in the evaluation .

Many of these conditions are progressive and neurodegenerative, with no treatment currently available. Identification of specific defects, such as ataxia with selective vitamin deficiency, provides treatment options for disorders that are eminently treatable. For other incurable disorders, such as Friedreich ataxia, treatment approaches such as antioxidant therapy may prolong life and lead to reduction in morbidity. Idebenone, a synthetic analogue of coenzyme Q has been tried with beneficial effects on ADL scores on both cardiac hypertrophy as well as neurologic symptoms in preliminary trials. Suitable doses have to be determined to optimize benefits. Supportive therapy, management of associated complications, and the role of support groups cannot be overemphasized for families who have to deal with truly challenging medical needs.

Support groups

- International Network of Ataxia Friends (INTERNAF)
- National Ataxia Foundation
2600 Fernbrook Lane; Suite 119
Minneapolis, MN 55447
Phone: 763-553-0020
Fax: 763-553-0167
Email: naf@ataxia.org
- Spinocerebellar Ataxia: Making an Informed Choice about Genetic Testing
- Euro-ataxia (European Federation of Hereditary Ataxias)
Boherboy, Dunlavin
Co Wicklow, Ireland
Phone: +353 45 401218
Fax: +353 45 401371
Email: mary.kearneyl@euro-ataxia.org
- NCBI Genes and Disease - Spinocerebellar ataxia
- WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 West 84th Street
New York, NY 10024
Phone: 800-437-MOV2 (800-437-6683)
Fax: 212-875-8389
Email: wemove@wemove.org

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Keywords

ataxia, abetalipoproteinemia, Angelman syndrome, arginase, argininemia, argininosuccinate lyase, argininosuccinate synthetase, argininosuccinic acidemia, ataxia telangiectasia, ataxia with selective vitamin E deficiency, ataxia with oculomotor apraxia, AOA, autosomal dominant ataxias, autosomal recessive ataxia, biotinidase deficiency, carbamyl phosphate synthetase deficiency, CPS deficiency, congenital disorders of glycosylation syndrome, cerebrotendinous xanthomatosis, Cockayne syndrome, CBS, Dandy Walker syndrome, defects of mitochondrial beta oxidation, dentatorubropallidoluysian atrophy, DRPLA, episodic ataxia type 1, EA1, episodic ataxia type 2, EA2, fragile X-associated tremor/ataxia syndrome, FXTAS

Friedreich's ataxia, Friedreich ataxia, GM2 gangliosidosis, Gaucher type III, Hartnup's disease, Hartnup disease, hypobetalipoproteinemia, Krabbe's globoid cell leukodystrophy, L-2 hydroxyglutaric acidemia, Lafora body disease, late infantile and juvenile sphingolipidoses, late infantile neuronal ceroid lipofuscinosis, late-onset urea cycle defects, Leigh's disease, Leigh disease, leukoencephalopathy with vanishing white matter, leukoencephalopathy with VWM, maple syrup urine disease, metabolic ataxias, metachromatic leukodystrophy, mitochondrial cytopathies, myoclonic epilepsy with ragged red fibers, MERRF

NARP syndrome, neuropathy ataxia retinitis pigmentosa, Niemann-Pick C disease, ornithine transcarbamylase deficiency, OTC deficiency, recessively inherited metabolic ataxias, Refsum's disease, Refsum disease, progressive myoclonic epilepsies, pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency, spinocerebellar ataxias, succinic-semialdehyde dehydrogenase deficiency, urea cycle defects, Unverricht-Lundborg disease, xeroderma pigmentosum, XP, metabolic disorder