INTRODUCTION

Hereditary metabolic disorders affect the nervous system on multiple levels, suggesting an inborn error or metabolic defect such as the following:
• Developmental delay
• Episodic alteration in level of consciousness or recurrent neurologic symptoms
• Family history of similar symptoms in a sibling or closely related individual
• Neurologic or developmental regression
• Multisystem involvement (in addition to neurologic systems)
• Presence of a particular neurologic sign

The development of ataxia is a neurologic sign that may provide a clue to the nature of the underlying disorder. Ataxia is defined as an inability to maintain normal posture and smoothness of movement. Interruption of afferent and efferent connections within the spinocerebellar system results in a broad-based gait (ataxic gait), scanning dysarthria, explosive speech, intention tremor, dysdiadochokinesia, dysmetria, and abnormalities of eye movements. Other neurologic symptoms and signs such as seizures and movement disorders 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, brainstem, and cerebral cortical involvement.

A wide range of molecular defects have been identified in which the spinocerebellar pathways are involved. However, the pathologic responses within the system are limited, resulting in a great deal of overlap in the clinical presentation. The disorders under consideration have a heritable basis; most follow an autosomal-dominant or autosomal-recessive pattern of inheritance and have an identified biochemical defect. This group of disorders is expanding constantly as the genetic defects underlying many of the recessively inherited ataxias are unraveled. For example, the molecular mechanism underlying Friedreich ataxia is due to a triplet repeat expansion, affecting the production of a protein called frataxin. The biochemical defect now is believed to result in impaired mitochondrial function.

**PATHOPHYSIOLOGY**

The spinocerebellar pathways principally are involved in most genetic ataxia syndromes. Lesions of the midline cerebellar vermis produce truncal and gait ataxia, while involvement of the lateral cerebellar hemispheres produces a limb ataxia. Other features of cerebellar involvement include scanning dysarthria, dysmetria, abnormalities of eye movements, and dysdiadochokinesia.

The pathologic bases of many clinically recognized phenotypes show considerable overlap. However, the genetic molecular and biochemical causes for these disorders are often distinct. The phenotypes may present with pure ataxia or involve multiple levels of the nervous system (including dementia, seizures, disturbance in proprioceptive function, movement disorders, and polymyoclonus).
Thus classification of these disorders is a daunting task, and no single method is entirely successful. In today’s molecular era, identification of genetic mutations has been instrumental in classifying these disorders, with the phenotype playing a secondary role.

GENETIC-BIOCHEMICAL BASIS FOR CLASSIFICATION

Early attempts to classify inherited ataxias were based on anatomic localization of pathologic changes (eg, spinocerebellar, pure cerebellar ataxias). 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. The last category was subdivided further into early onset (<20 y) and late-onset (>20 y) subtypes.

This article outlines inherited ataxias with a known biochemical defect and uses biochemical defects as an anchor with which to classify these various disorders. The molecular genetic explanations for the autosomal-dominant spinocerebellar ataxias rapidly are being unraveled, although the precise pathogenesis is not clearly understood in many of these disorders. Although ataxia is a prominent feature of all these disorders, the presentation can be variable (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.

- **Triplet repeat expansions**

This new 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 and earlier age of onset in successive generations in many 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.

- **Mitochondrial DNA defects**

Since mitochondria were established to carry their own functional genome, a new mechanism of genetic nonmendelian inheritance, maternal inheritance, was discovered. All the mitochondria in the newly formed zygote are derived from the ovum (ie, maternally derived). Mitochondrial DNA is more vulnerable to mutations in the oxidizing environment.
of mitochondria; 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. Mild 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, thereby partially explaining the neurologic involvement in many mitochondrial disorders.

- **Classification**

In this chapter, the disorders are classified as follows:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute intermittent ataxia</td>
<td></td>
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<tr>
<td>Ataxias with polymyoclonus and seizures</td>
<td></td>
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<tr>
<td>Ataxias with spinocerebellar dysfunction</td>
<td></td>
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<tr>
<td>Progressive ataxias plus (ie, prominent cerebellar dysfunction with additional neurologic signs)</td>
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</tbody>
</table>

**ACUTE INTERMITTENT ATAXIAS**

- **Maple Syrup Urine Disease (Intermittent Form)**

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

- **Clinical features**
  - Characteristic urine odor
  - Intermittent bouts of ataxia and neurologic obtundation progressing to coma
  - Possibly mental retardation and motor delay in intermediate form

- **Biochemical abnormalities**
  - 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-allo-isoleucine in body fluids (pathognomonic)
Treatment

- 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.

Episodic Ataxia 1

Episodic ataxia 1 (EA1) is a rare autosomal-dominant disorder and represents a channelopathy. It is caused by point mutations that affect the human voltage-gated potassium channel gene on band 12p13.

- 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 features
  - 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

Episodic ataxia 2 (EA2) is an autosomal-dominant disorder that has been associated with mutations that affect the calcium channel (CACNA1A) gene at the 19p13 locus. It is allelic to familial hemiplegic migraine and spinocerebellar ataxia type 6 (SCA6), wherein mutations affecting the same gene have been described.

- 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
- Investigation
- No specific diagnostic test is available.
  - **Treatment**
    - Some patients with EA2 may respond to acetazolamide.
- **Hartnup Disease**

This autosomal-recessive disorder is caused by defective intestinal transport and renal tubular reabsorption of neutral amino acids (primarily tryptophan). The reduced availability of tryptophan may lead to a secondary deficiency of the vitamin niacin (nicotinic acid). The gene locus is 11q13. Incidence based on neonatal screening data is estimated at 1 in 30,000.

  - **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 features**
    - Excessive excretion of monoamino-monocarboxylic amino acids in urine
    - Urinary indoxyl derivatives (5-hydroxyindoleacetic acid) also excreted in urine; may be demonstrated 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**

Pyruvate dehydrogenase (PDH) deficiency is an X-linked recessive disorder that affects a mitochondrial multienzyme complex, which in turn inhibits the conversion of pyruvate to acetyl-CoA.

The enzymatic complex consists of 3 enzymes. The pyruvate dehydrogenase has 4 subunits, with the E1 alpha1 subunit most often affected. Inheritance is X linked.

**Clinical features**

- Many present in early infancy with a catastrophic neurologic picture of hypotonia, lactic acidosis, and seizures (associated with cerebral malformations)
- Benign late-infantile variant also known to occur
- Episodic ataxia
- Normal mental and motor development
- Postexercise fatigue
- Transient paraparesis

**Laboratory investigations**

- Serum and CSF lactic acidosis (characteristic)
- Reduced PDH activity in muscle biopsy
- Multiple areas of necrosis in the gray matter, white matter, and basal ganglia on imaging studies in prenatal and early infantile form
- Limited information concerning late benign presentations of this disorder

Postmortem and autopsy in one affected male who died when aged 50 years showed findings of cerebellar degeneration and lesions around the third ventricle and cerebral aqueduct. This case suggests findings that are consistent 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. Ketogenic diet has been effective in some patients. Treatment of lactic acidosis by dichloroacetate also 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 to less than 20% of baseline levels but above 5 mmol/L, 2 additional doses may be tried.
- Published open trials on the drug indicated improved survival (with reduced morbidity) in responders. However, questions remain regarding the efficacy of this treatment.

**Pyruvate Carboxylase Deficiency**

This most common disorder of pyruvate metabolism is an autosomal-recessive inherited deficiency of pyruvate carboxylase. Identified mutations affect the gene locus on chromosome 11 (11q13.4-q13.5). It usually presents in the neonatal period with severe lactic acidosis or in early infancy with features similar to PDH deficiency with psychomotor retardation, hypotonia, and seizures. A benign variant with intermittent ataxia and normal development also has been reported.

**Laboratory features**

- Lactic acidosis (elevated plasma lactate)
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 also reported in the neonatal form on magnetic resonance imaging (MRI)
- Can be confirmed by assay for enzyme activity in cultured fibroblasts

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.

Fatty Acid Oxidation Defects

Recessively inherited defects that affect mitochondrial beta-oxidation can result in intermittent episodes of neurologic symptoms (eg, weakness, ataxia, coma) in affected individuals. Examples of such defects are as follows:

- Carnitine palmitoyltransferase-I deficiency
- Long-chain acyl-CoA dehydrogenase deficiency
- Medium-chain acyl-CoA dehydrogenase deficiency
- 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

Clinical features

- Episodic vomiting
- Intermittent bouts of weakness, lethargy, ataxia, and coma
- Neurologic symptoms induced by fasting

Laboratory features

- 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
- Specific enzyme assays on cultured skin fibroblasts
Increased dicarboxylic aciduria (suberic, sebacic, adipic acids) upon urinary organic acid analysis

**Treatment**

- Avoidance of prolonged fasting
- Carnitine supplementation in doses of 50-100 mg/kg/d
- Adequate caloric intake through intravenous glucose or nasogastric cornstarch-based formula
- Substitution of dietary fat with medium-chain triglycerides (may be helpful in bypassing metabolic block in these disorders)

**Urea Cycle Defects**

Defects of each of the 5 enzymes of the urea cycle and 1 of its activators have been described. Most present with hyperammonemic coma in the neonatal period. Partial deficiencies can result in delayed presentation or intermittent symptoms during periods of decompensation.

The 5 urea cycle enzymes are as follows:

- Carbamyl phosphate synthetase
- Ornithine transcarbamylase (X-linked inheritance)
- Argininosuccinate synthetase
- Argininosuccinate lyase
- Arginase

Four of the 5 enzyme deficiencies (excepting ornithine transcarbamylase) are inherited as autosomal-recessive defects.

**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 are reported.
  - Clinical symptoms may first present in ornithine transcarbamylase heterozygotes during pregnancy.
  - Examination findings may demonstrate hyperactive deep tendon reflexes, papilledema, and decerebrate or decorticate posturing.
  - The clinical picture in cases of argininemia may mimic spastic diplegic cerebral palsy.
Laboratory features

- 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
- Elevated plasma ammonium (ionized form at physiologic pH)
- Enzyme assays on liver biopsies and DNA analysis (can be confirmatory)
- Respiratory alkalosis

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, phenylbutyrate)
- Orthotopic liver transplant (another therapeutic option)

Table 1. Intermittent Ataxias

<table>
<thead>
<tr>
<th>Autosomal-Dominant/Recessive Ataxias</th>
<th>Neurologic Phenotype</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maple syrup urine disease</td>
<td>Intermittent ataxia</td>
<td>AR*, 19q13.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mutations affecting 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</td>
</tr>
<tr>
<td>Episodic ataxia (EA-1)</td>
<td>Intermittent ataxia</td>
<td>AD†, 12p13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Missense point mutations affecting the voltage-gated potassium channel (KCNA1)</td>
</tr>
<tr>
<td>Condition</td>
<td>Clinical Features</td>
<td>Genetics</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Episodic ataxia (EA-2)</td>
<td>Intermittent ataxia</td>
<td>AD, 19p13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Point mutations or deletions also allelic with SCA-6 and hemiplegic migraine</td>
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<tr>
<td></td>
<td></td>
<td>• Altered calcium channel function</td>
</tr>
<tr>
<td>Hartnup disease</td>
<td>Intermittent ataxia</td>
<td>AR, 11q13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Abnormality in the intestinal and renal transport of neutral alpha amino acids</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase deficiency</td>
<td>Intermittent ataxia, Lactic acidosis</td>
<td>X-linked recessive (Xp22.2-p22.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Defective E1 component of the PDH complex</td>
</tr>
<tr>
<td>Pyruvate carboxylase deficiency</td>
<td>Intermittent ataxia, Lactic acidosis</td>
<td>AR 11q13.4-q13.5</td>
</tr>
<tr>
<td>Defects of mitochondrial fatty acid beta oxidation</td>
<td>Intermittent ataxia, Metabolic acidosis, Hyperammonemia</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multiple defects affecting different acyl-CoA dehydrogenases</td>
</tr>
<tr>
<td>Late-onset urea cycle defects</td>
<td>Intermittent ataxia, Episodic encephalopathy</td>
<td>AR, X-linked inheritance for OTC‡</td>
</tr>
<tr>
<td>• Argininosuccinic acidemia</td>
<td></td>
<td>• 7q21.3-q22 (argininosuccinate lyase)</td>
</tr>
<tr>
<td>• CPS§ deficiency</td>
<td></td>
<td>• 2q33-q36 (carbamoyl phosphate synthetase I)</td>
</tr>
<tr>
<td>• Citrullinemia</td>
<td></td>
<td>• 9q34 (argininosuccinate</td>
</tr>
</tbody>
</table>
The following disorders are dominantly or recessively inherited. They present 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. SCA 1, 2, 3, 6, and 7 and dentatorubropallidoluysian atrophy (DRPLA) are caused by dynamic mutations that affect tandem triplet nucleotide repeats. Table 3 summarizes the salient phenotypic features and the degree of triplet repeat expansions necessary to produce pathologic symptoms. Such expansions code for polyglutamine tracts, which are responsible for progressive neuronal degeneration.

**Autosomal-Dominant Cerebellar Ataxias**

The nomenclature for the autosomal dominant hereditary ataxias has varied over the years. Terms no longer used to refer to SCA1 include Marie's ataxia, atypical Friedreich's ataxia, and olivopontocerebellar atrophy. At least 12 forms of dominantly inherited spinocerebellar ataxias have been described and labeled sequentially from SCA1 to SCA12. The position 9 has been reserved for a hitherto unknown variety.
A great degree of overlap in phenotype is present, with the major group of symptoms related to cerebellar and spinocerebellar pathway dysfunction. Other than a few specific distinguishing features described in Table 3, clinical and neuroimaging studies are nonspecific. Most of the triplet expansions affect CAG repeats; in the SCA8 form, a CTG expansion is involved.

Table 3. Progressive Ataxias With Spinocerebellar Dysfunction

<table>
<thead>
<tr>
<th>Autosomal-Dominant Ataxias</th>
<th>Neurologic Phenotype*</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinocerebellar ataxia (SCA-1)</td>
<td>Peripheral neuropathy, Pyramidal signs</td>
<td>6p23 Ataxin-1, CAG expansion 39-83 (6-36 normal range)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-2)</td>
<td>Abnormal ocular saccades, Hyporeflexia, dementia, Peripheral neuropathy</td>
<td>12q24.1 Ataxin-2, CAG expansion 34-400 (15-31 normal range)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA-3)</td>
<td>Pyramidal, extrapyramidal, and ocular movement abnormalities</td>
<td>14q24.3-q32.2 CAG expansion 55-86 (12-40 normal range)</td>
</tr>
<tr>
<td>Spinocerebellar ataxia (SCA)</td>
<td>Amyotrophy and sensory neuropathy</td>
<td>16q22.1</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Sensory axonopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myokymia, nystagmus, and altered vibration sense</td>
<td>11p11.q11</td>
<td>CAG expansion not demonstrated as yet</td>
</tr>
<tr>
<td>Slowly progressive ataxia</td>
<td>19p13</td>
<td>CAG expansion 20-33 (4-16 normal range) with altered alpha1A subunit of the voltage-dependent calcium channel (CACLNIA4)</td>
</tr>
<tr>
<td>Visual loss retinopathy</td>
<td>3p21.1-p12</td>
<td>Ataxin-7, CAG expansion 37 to greater than 300 (4-19 normal range)</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>13q21</td>
<td>CTG expansion 100-250 (16-34 normal range)</td>
</tr>
<tr>
<td>Ataxia, nystagmus, and seizures</td>
<td>22q13</td>
<td>(genetic anticipation in families suggests triplet expansion)</td>
</tr>
<tr>
<td>Mild disorder ataxia</td>
<td>15 q14-q21.3</td>
<td>Mutation not identified</td>
</tr>
<tr>
<td>Pure spinocerebellar ataxia</td>
<td>5q31-q33</td>
<td>Protein phosphatase PPP2R2B gene, CAG expansion 66-78 (6-26 normal range)</td>
</tr>
<tr>
<td>Progressive ataxia</td>
<td>12p13.31</td>
<td></td>
</tr>
</tbody>
</table>
atrophy (DRPLA) | plus chorea, seizures, myoclonus, and dementia | Triplet repeat expansion leading to altered protein product Atrophin-1 with toxic gain of function

*Gait ataxia is a constant feature*

Spinocerebellar ataxia (SCA-1) (Olivopontocerebellar atrophy)

**Clinical features include the following:**

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

**Figure 2.** Olivopontocerebellar degeneration. A, The axial T1-weighted scan at the level of the fourth ventricle demonstrates loss of the normal olivary bulge bilaterally (arrows) and atrophy of the middle cerebellar peduncles. Pontine and cerebellar atrophy is noted on additional axial (B) and sagittal (C) T1-weighted scans.
Figure 3. A case with olivopontocerebellar atrophy

Figure 4. Olivopontocerebellar atrophy (olivopontocerebellar degeneration, olivopontine cerebellar degeneration, spinocerebellar degeneration type I, spinocerebellar ataxia type I) is an autosomal dominant inherited degenerative disorder of the central nervous system that predominantly involves neurons in the cerebellum, inferior olives in the brain stem, and tracts in the spinal cord. The condition results from CAG trinucleotide repeats within the ATX1 gene that encodes for the ataxin. Normal individuals contain 19-36 of the CAG repeats within the gene; affected persons have 40-81 CAG repeats. The disease is manifest by ataxia, an intention tremor, rigidity, loss of deep tendon reflexes, and a loss of vibration and pain sensation. Alpha synuclein is present in neuroglia and neurons of persons with olivopontocerebellar atrophy. The pons becomes markedly atrophic. Several genetically distinct types of olivopontocerebellar atrophy are recognized (olivopontocerebellar atrophy type I, olivopontocerebellar atrophy type II, olivopontocerebellar atrophy type III, and olivopontocerebellar atrophy type IV). Nystagmus occurs in these disorders and other ophthalmic manifestations, such as retinal degeneration and progressive ophthalmoplegia occur in some of these conditions, such as olivopontocerebellar atrophy type III.
Spinocerebellar ataxia (SCA-2)

Clinical features include the following:

- Age of onset - 2-65 years
- Ataxia, facial fasciculation, lid retraction, reduced ocular saccadic velocity
- SCA 2 protein product termed ataxin 2

Spinocerebellar ataxia (SCA-3)

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

Clinical features include the following:

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

Spinocerebellar ataxia (SCA-4)

This disorder is linked tightly to 16q22.1 locus. Molecular basis has not yet been delineated.

Clinical features include the following:

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

Spinocerebellar ataxia (SCA-5)

Gene locus is the 5 cM candidate region on chromosome 11 in open reading frame of unknown gene. No expansion has been detected yet.

Clinical features include the following:

- Cerebellar ataxia, facial myokymia, impaired vibration sense; 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 (SCA-6)

Gene locus is the triplet expansion repeat affecting the 19p13 locus. The size of the expansion in affected individuals is 21-27. The mutation affects the calcium channel \textit{CACNLA1A}.

Clinical features include the following:

- 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

Spinocerebellar ataxia (SCA-7)


Clinical features include the following:

- Ophthalmoplegia, dysarthria, pyramidal and extrapyramidal signs, and impaired vibration sense
- Visual loss due to macular retinal degeneration (unique finding in this disorder)

Spinocerebellar ataxia (SCA-8)

This disorder is linked to an untranslated CTG expansion on 13q21.

Clinical features include the following:

- 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 (SCA-10)

Gene locus is 8.8 cM candidate region on chromosome 22q13-ter.

Clinical features include the following:

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

**Spinocerebellar ataxia (SCA-11)**

Linkage is established to 15q14-q21.3.

**Clinical features include the following:**

- 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 (SCA-12)**

- Gene locus is a CAG expansion with a range of 66-78 repeats at 5q31-q33 locus. This expansion codes for a brain-specific regulatory subunit of the protein phosphatase PP2A.

**Clinical features include the following:**

- Tremor in early stages
- Later development of a pure spinocerebellar ataxia

**Dentatorubropallidoluysian atrophy**

DRPLA is another triplet-repeat neurodegenerative disorder with dominant inheritance and genetic anticipation. The size of the expansion in affected individuals varies from 49-75 repeats. The mutation is believed to affect a protein product "atrophin-1," resulting in a toxic gain of function for the altered protein; the protein includes a serine repeat, a region of alternating acidic and basic amino acids, and the variable polyglutamine repeat.

The condition is allelic to the Haw River syndrome reported in African Americans. 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 include ataxia, dementia, polymyoclonus, and chorea. No specific findings are reported on imaging studies. Molecular genetic confirmation by DNA analysis is possible. No treatment is available.

**Laboratory features**

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 2. Progressive Ataxias With Spinocerebellar Dysfunction

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>1° Testing</th>
<th>2° Testing</th>
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<tbody>
<tr>
<td>Cerebellar ataxia, Pure</td>
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<td>SCA11, SCA14, SCA15, SCA16, SCA22</td>
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<td>SCA1, SCA7</td>
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<tr>
<td>Peripheral neuropathy</td>
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Cortical disorders

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</thead>
<tbody>
<tr>
<td>Dementia</td>
<td>SCA17, DRPLA</td>
<td>SCA2, SCA13, SCA19, SCA21</td>
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<tr>
<td>Psychosis</td>
<td>DRPLA, SCA17</td>
<td>SCA3, SCA-FGF14 (Episodic)</td>
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Movement disorders

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<td>Chorea</td>
<td>DRPLA, SCA17</td>
<td>SCA1 (Late stage)</td>
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<td>Myoclonus</td>
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Ocular disorders

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<tr>
<td>Ophthalmoplegia</td>
<td>SCA3,</td>
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Autosomal-Recessive Cerebellar Ataxias

- **Friedreich Ataxia**

The prototype disorder of familial spinocerebellar degeneration, FRDA was the first identified recessively inherited condition with a mutation involving a triplet repeat expansion.

Ninety-six percent of patients with FRDA1 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 greater 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 this GAA trinucleotide repeat expansion in the X25 gene.

- **The mutation leads to formation of the abnormal protein termed frataxin.**
  - The cells carrying this mutation appear to be sensitive to oxidative stress.
  - Apparently this disease has more than 1 locus.
  - Great phenotype variance exists among affected individuals, even within the same family; the types have been divided arbitrarily into late-onset FRDA (LOFA onset, 25-39 y) and very late-onset FRDA (VLOFA, onset >40 y). Deep tendon reflexes are retained and progression is very slow, particularly in Acadians.
  - These variants have been found to have generally shorter GAA expansions (<600) in at least 1 of the 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**
  - Variable age of onset when younger than 20 years
- Neurologic - Cerebellar ataxia, dysarthria, nystagmus, uncoordinated limb movements, hypoactive knee and ankle deep tendon reflexes, Babinski sign, impaired position sense, and impaired vibratory sense
- Cardiac - Symmetric, concentric, hypertrophic cardiomyopathy; congestive heart failure; and subaortic stenosis
- Skeletal - Pes cavus, scoliosis, and hammer toe
- Metabolic - Abnormal glucose tolerance test, diabetes mellitus, and diabetic ketosis

- **Laboratory features**
  - Abnormal electrocardiogram
  - Abnormal echocardiogram
  - Abnormal motor and sensory nerve conduction
  - MRI - Cerebellar atrophy and a thin spinal cord
  - Evidence of iron accumulation within mitochondria of FRDA fibroblasts subjected to oxidative stress, resulting in impaired respiratory function

- **Treatment**
  - No specific treatment other than symptomatic and supportive care is available.

- **More details about Friedreich Ataxia**

The major pathophysiologic finding in FA is a "dying back phenomena" of axons, beginning in the periphery with ultimate loss of neurons and a secondary gliosis. The primary sites of these changes are the spinal cord and spinal roots. There is a loss of large myelinated axons in peripheral nerves, which increases with age and disease duration. Unmyelinated fibers in sensory roots and peripheral sensory nerves are spared.

![Figure 5. Myelin staining is often used to demonstrate areas of axonal loss, as loss of myelin is much easier to appreciate than axonal loss. In Friedreich ataxia, degeneration can be identified in the spinal cerebellar tracts laterally and the ascending sensory tracts medially.](image)

The posterior columns, corticospinal, ventral, and lateral spinocerebellar tracts all show demyelination and depletion of large myelinated nerve fibers to differing extents. This is accompanied by a fibrous gliosis that does not replace the bulk of the lost fibers. Overall,
the spinal cord becomes thin and the anteroposterior (AP) and transverse diameters of the thoracic cord are reduced. The dorsal spinal ganglia show shrinkage and eventual disappearance of neurons associated with proliferation of capsular cells. The posterior column degeneration accounts for the loss of position and vibration sense and the sensory ataxia. The loss of large neurons in the sensory ganglia causes extinction of tendon reflexes.

Large neurons of the dorsal root ganglia, especially lumbosacral, and nerve cells in Clarke's column are reduced in number. The posterior roots become thin. The dentate nuclei exhibit mild to moderate neuronal loss and the middle and superior cerebellar peduncles are reduced in size. There is patchy loss of Purkinje cells in the superior vermis of the cerebellum and of neurons in corresponding portions of the inferior olivary nuclei. There are mild degenerative changes in the pontine and medullary nuclei and optic tracts. The cerebellar ataxia is explained by loss of the lateral and ventral spinocerebellar tracts, involvement of Clarke's column, the dentate nucleus, superior vermis, and dentatorubral pathways.

The corticospinal tracts are relatively spared down to the level of the cervicomedullary junction. Beyond this point, the corticospinal tracts are severely degenerated, which becomes progressively more severe moving down the spinal cord. This explains the common finding of bilateral extensor plantar responses and weakness late in the disease. Loss of cells in the nuclei of cranial nerves VIII, X, and XII results in facial weakness, speech, and swallowing difficulty.

Myocardial muscle fibers also show degeneration and are replaced by macrophages and fibroblasts. Essentially, chronic interstitial myocarditis occurs with hypertrophy of cardiac muscle fibers; fibers become hypertrophied and lose their striations. This is followed by swelling and vacuolation and finally interstitial fibrosis. The nuclei appear hyperchromatic and occasionally vacuolated. The cytoplasm appears granular with frequent lipofuscin depositions. Kyphoscoliosis is likely, secondary to spinal muscular imbalance.

Figure 6. Friedreich Ataxia
Histologic Findings in Friedreich ataxia

A cross-section through the lower cervical cord clearly shows loss of myelinated fibers of the dorsal columns and the corticospinal tracts (Weil stain). Milder involvement of spinocerebellar tracts is also present. The affected tracts show compact fibrillary gliosis (hematoxylin and eosin [H&E]) but no breakdown products or macrophages, reflecting the very slow rate of degeneration and death of fibers. The dorsal spinal ganglia show shrinkage and eventual disappearance of neurons associated with proliferation of capsular cells (H&E). The posterior roots are nearly devoid of large myelinated fibers. Within the thoracic spinal cord, degeneration and loss of cells of the Clarke column is apparent.

Figure 7. Friedreich Ataxia, Spinal cord

Neuroimaging in Friedreich ataxia

In Friedreich ataxia MRI examination shows cervical cord atrophy, thinning with reduced anteroposterior diameter. A hyperintense line on the posterior portion of cord is commonly seen, which represents loss of myelinated fibers and gliosis. The thinned spinal cord is seen lying on the posterior wall of spinal canal with increased signal intensity in its posterior and lateral compartments.
Figure 8. MRI of the brain in a case with Friedreich ataxia showing normal findings

Figure 9. MRI T2 (A,B) and MRI T1 (C) in a case with Friedreich's ataxia showing marked atrophy of the uppermost part of the cervical spinal cord

Figure 10. MRI T1 (A) and MRI T2 (B) in a case with Friedreich's ataxia showing marked atrophy of the uppermost part of the cervical spinal cord
Figure 11. MRI T2 images in a case with Friedreich's ataxia showing cervical cord atrophy, thinning with reduced anteroposterior diameter. Notice the hyperintense line in posterior portion of cord. The thinned spinal cord is seen lying on the posterior wall of spinal canal with increased signal intensity in its posterior and lateral compartments. The anterior subarachnoid space is enlarged. The intramedullary signal changes reflect loss of myelinated fibers and gliosis.

The decreased anteroposterior diameter of the spinal cord at the upper cervical region confirms that atrophy of the upper cervical part of the spinal cord is a characteristic feature of Friedreich’s ataxia, as opposed to other forms of corticocerebellar and cerebellar-brainstem atrophy. This had been indicated on the basis of subjective evaluation in two previous studies.

No direct pathologic correlation of the intramedullary signal abnormalities is available. However, the sensitivity of MR imaging to degeneration of white matter tracts in the brain and spinal cord after stroke or in degenerative diseases of the CNS - that is manifested on the MRI T2 images as hyperintense lines- has been cited in several reports [1-5]. Because of the substantial similarities between the intramedullary signal abnormality pattern that is found in patients with Friedreich and the distribution of demyelination and gliosis of white matter tracts in the histopathologic pictures of the spinal cord in cases of Friedreich’s ataxia, we think it reasonable to assume that the MR appearance could reflect these pathologic findings. Obviously, the intramedullary signal abnormality pattern is not exclusive to Friedreich’s ataxia and can be observed in subacute combined degeneration, tabes dorsalis, wallerian degeneration, and AIDS myelopathy. In these conditions, however, associated clinical and laboratory findings usually allow the correct diagnosis. [22-25]
Scoliosis is common in Friedreich's ataxia. Detection of signal changes in the white matter tracts of the spinal cord of patients with Friedreich’s ataxia could be an index of severity or progression of the disease and in this respect it is more useful than cord atrophy. The association between the extent of intramedullary signal changes and the chronicity and severity of disease is well known by the author and was reported by others [22-25]. Although this analysis could be informative, it requires quantitation of the signal changes in the white matter tracts and evaluation of the thoracolumbar spine. Noteworthy is the fact that intramedullary signal changes are only in patients with Friedreich’s ataxia. No such findings were seen in any of the patients with corticocerebellar or cerebellar-brainstem atrophy in the author experience and by others [22-25]. Thus, it appears that evaluation of the cervical spinal cord for intramedullary signal changes might be useful for differential diagnosis in patients with progressive ataxia of uncertain clinical type.

In a broad sense, MR examination of the cervical spinal cord is more informative than examination of the brain in patients with Friedreich’s ataxia. Although spinal cord atrophy and intramedullary signal changes theoretically could be searched for in the thoracic spinal cord of patients with Friedreich’s’ ataxia, focusing on the cervical spinal cord is recommended because it usually allows concurrent evaluation of the brainstem and the cerebellum. This may help in the differential diagnosis with corticocerebellar and cerebellar-brainstem atrophies.

In conclusion, MR imaging of the cervical spinal cord can show thinning of the cord and intramedullary signal changes consistent with degeneration of white matter tracts in the
lateral and posterior columns of patients with Friedreich’s ataxia. These MR findings might be helpful for differential diagnosis in patients with progressive ataxia of uncertain clinical type.

- **Abetalipoproteinemia**

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, which results in dysfunction.

  - **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 most patients
    - Pigmentary retinopathy
  - **Laboratory features**
    - 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
  - **Treatment**
    - High-dose supplementation of vitamin E has a beneficial effect on neurologic symptoms.
    - Administer other fat-soluble vitamins (D, A, K).

- **Hypobetalipoproteinemia**

This autosomal-dominant disorder is clinically indistinguishable from abetalipoproteinemia.

It is caused by mutations that affect the *Apo-B* gene, which affects turnover of apolipoprotein B.

Neurologic and nonneurologic manifestations are similar in homozygotes. Heterozygotes, on occasion, also may be affected.
• **Ataxia With Selective Vitamin E Deficiency**

This is a rare autosomal-recessive disorder resulting from a mutation that affects the gene for alpha-tocopherol transfer protein.

  o **Clinical features**

It is phenotypically similar to Friedreich ataxia (FRDA), with head titubation (28%), spinocerebellar ataxia, areflexia, and propioception loss.

Skin is affected by xanthelasmata and tendon xanthomas.

Onset varies from ages 2-52 years and usually occurs when younger than 20 years; it slowly progresses over decades.

  o **Laboratory features**

Measurements include low-to-absent serum vitamin E and high serum cholesterol, triglyceride, and beta-lipoprotein.

  o **Treatment**

Treatment consists of vitamin E supplementation. A dose of 400-1200 IU/d improves neurologic function. This should be maintained for life.

**ATAXIAS WITH PROGRESSIVE CEREBELLAR DYSFUNCTION PLUS SYSTEMIC FEATURES**

These disorders present with progressive ataxia combined with other neurologic dysfunction and systemic features that depend on the underlying pathology. The clinical features may include a varying combination of cognitive delay or decline, abnormalities of muscle tone, seizures, and movement disorders. The mode of inheritance varies and includes both mendelian and nonmendelian patterns. Many of the disorders discussed involve defects in DNA repair that involve a complex sequence of events. In disorders involving these pathways, multiple gene defects are involved.

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

Autosomal-dominant (CSB) and recessive (CKN1) forms have been reported. Defective repair of transcriptionally active DNA is the underlying basis of the disorder. Cultured skin fibroblasts from these patients display abnormal UV sensitivity.

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
- Wizened facies (similar to progeria)

Laboratory features

Calcification of basal ganglia is found on CT scan, and white matter changes are found on MRI.

Treatment

No treatment is available; early death in the second or third decade is usual.

Xeroderma Pigmentosum

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.

Clinical features

- Ataxia, chorea, and axonal polyneuropathy
- Cutaneous photosensitivity and multiple cancers
- Mental and motor retardation
- Microcephaly
- Sensorineural deafness

Treatment

No treatment is available.
Ataxia Telangiectasia

This progressive, recessively inherited ataxia presents 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.

A defective truncated protein (possibly phosphatidylinositol-3 kinase) results from mutations that affect the ATM gene locus.

The disease begins when patients are aged 1-3 years.

Clinical features

- Choreoathetosis
- Cutaneous and bulbar telangiectasia
- Immunodeficiency and increased susceptibility to infections
- Oculomotor apraxia
- Progressive ataxia and slurred speech
- Susceptibility to cancer (eg, leukemia, lymphoma)

Laboratory features

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 in 90-95% of patients
- Abnormality in colony survival assay, the ability of colony formation of a lymphoblastoid cell line following irradiation
- Karyotyping abnormalities involving 7-14 chromosomal translocation in 5-15% of cells after phytohemagglutinin stimulation of lymphocytes in peripheral blood
- Breakpoints involved in translocation at the 14q11 and 14q32 sites

Treatment

No treatment is available other than supportive care and careful management of complications with modified chemotherapy.

Refsum Disease

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 abnormalities (arrhythmia)

**Laboratory features**

- 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**

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, seizures
- Peripheral neuropathy
- Progressive ataxia with mental decline
- Pseudobulbar palsy
- Tendon xanthomas, cataracts

**Laboratory features**

- Elevated cholestanol and apolipoprotein 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. HMG-CoA reductase inhibitor also can be added to inhibit cholesterol biosynthesis.
Biotinidase Deficiency

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 features

- Can be demonstrated by assay in serum leukocytes or cultured fibroblasts
- Hyperammonemia
- Hypoglycinemia
- Metabolic acidosis, lactic acidosis
- Possible intermittent organic aciduria (excess excretion of metabolites such as hydroxyisovaleric acid, methylcrotonylglycine, hydroxypropionate, and methylcitrate in the urine) as demonstrated by mass spectrometry

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.

Late-Onset Sphingolipidoses

These complex biochemical defects are related to specific deficiencies of lysosomal enzymes (see Table 4). 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. As these disorders are progressive, symptoms and signs can be seen in combination. The disorders are autosomal recessive. Skin examination under electron microscope is an effective screening tool. Definitive diagnosis can be established by lysosomal enzyme assay in leukocytes or cultured skin fibroblasts.
L-2-hydroxyglutaric aciduria

This autosomal-recessive inherited defect is characterized by excessive excretion of L-2-hydroxyglutaric acid in the urine. The precise molecular basis not well established.

Clinical features

- Presence of cognitive delay and epileptic seizures
- Age of onset of 6-20 years
- 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

Treatment

No treatment is available.

Carbohydrate Deficient Glycoprotein Syndrome

Carbohydrate deficient glycoprotein syndrome (CDG) is a new class of disorders that results from abnormalities of carbohydrate-deficient glycoproteins, particularly transferrin. The disorder has been reported from Scandinavian countries as well as other European countries. All are autosomal-recessive conditions; several clinical and biochemical types have been characterized. CDG is caused by mutations affecting the enzyme phosphomannomutase; the gene locus is located on subband 16p13.3.

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, and inverted nipples (considered characteristic clinical features)
- In the teenage years, evident lower limb atrophy and peripheral neuropathy
- Presents in infancy (first year)
- Severe mental retardation and hypogonadism recognized in later years

Laboratory features

- Decreased serum glycoproteins
- MRI showing striking pontocerebellar atrophy
- Reduced thyroxine-binding globulin levels
Reduced N-acetylglucosaminyltransferase
Sialic acid, galactose, and N-acetylglucosamine deficiency in total serum glycoproteins
Synthesized proteins with fewer attached carbohydrate moieties than normal glycoproteins.
When an electric field is applied to serum, proteins tend to separate based on charge.
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 is considered diagnostic for this disorder.

### Treatment

No treatment is available other than supportive care.

#### Leukoencephalopathy With Vanishing White Matter

Leukoencephalopathy with vanishing white matter (VEM) is a recently described disease entity presenting with leukoencephalopathy of unknown origin. The disorder has an autosomal-recessive inheritance with an age-dependent penetrance.

The gene is located on band 3q27; the disease gene, its function, and mutations causing the disease remain to be identified.

#### 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 features

- 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.

**Treatment**

No effective treatment is known to halt progression of the disorder, although symptomatic and supportive measures can improve the quality of life.

**Succinic-Semialdehyde Dehydrogenase Deficiency**

Succinic-semialdehyde dehydrogenase deficiency (SSADH) is a recessively inherited disorder affecting the 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 features**

- 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.

**Neuropathy, Ataxia and Retinitis Pigmentosa, and Peripheral Neuropathy Syndrome**

Neuropathy, ataxia and 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 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

This disorder has a distinct neuropathologic picture, a highly variable clinical presentation, and 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 brain stem, thalamus, and cerebellum; the most important of these are as follows:
    - Oculomotor - Nuclear or supranuclear ophthalmoplegia; central nystagmus with rotary and horizontal components
    - Relapsing-remitting course, rarely progressively fatal
    - Respiratory - Characterized by unexplained hyperventilation, apnea, and irregular respiration (air hunger)
    - Truncal ataxia, incoordination, and intention tremor evident as child begins to walk

- Laboratory features
  - Characteristic lesions, which are symmetric, can be demonstrated in the thalamus, putamen, and globus pallidus on T2-weighted MRI sequences. The lesions also are distributed in the brain stem 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 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 B supplementation has been administered without documented benefit.
Recently, the ketogenic diet has been reported to be useful in treating patients with pyruvate dehydrogenase complex deficiency.

### Table 4. Ataxias With Progressive Cerebellar Dysfunction Plus Systemic Features

<table>
<thead>
<tr>
<th>Autosomal-Dominant/Recessive Ataxias</th>
<th>Neurologic Phenotype</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cockayne syndrome (CSB)</strong></td>
<td>Progressive ataxia plus</td>
<td>AD*, 10q11-q21&lt;br&gt;• DNA excision-repair cross-complementing (<em>ERCC6</em>) gene defect</td>
</tr>
<tr>
<td><strong>Xeroderma pigmentosum</strong></td>
<td>Progressive ataxia plus</td>
<td>AR†&lt;br&gt;• Genetically heterogeneous with several identified complementation groups&lt;br&gt;• Mutations resulting in either defective damage specific DNA-binding protein or defective excision repair&lt;br&gt;• Neurologic manifestations beginning in childhood relating to complementation Gp. A 9q34 locus&lt;br&gt;• Other complementation groups involved - 2q21 (B &amp; CS); 3p25.1 (C); 19q13.2(D); Unknown (E); 16p13 (F); 13q32-33 (G &amp; CS)</td>
</tr>
<tr>
<td><strong>Ataxia telangiectasia</strong></td>
<td>Progressive ataxia plus</td>
<td>AR, 11q22-q23&lt;br&gt;• Mutation resulting in truncated protein and dominant negative defect</td>
</tr>
</tbody>
</table>

### Recessive Metabolic Ataxias

<table>
<thead>
<tr>
<th>Neurologic Phenotype</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Refsum disease</strong></td>
<td>AR, 10pter-p11.2&lt;br&gt;• Mutations affecting gene coding for phytanoyl-CoA hydroxylase</td>
</tr>
<tr>
<td><strong>Cerebrotendinous xanthomatosis</strong></td>
<td>AR, 2q3-pter&lt;br&gt;• Defective mitochondrial cytochrome-</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical Features</th>
<th>Chromosome Location</th>
<th>Genetic Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotinidase deficiency</td>
<td>Progressive ataxia plus</td>
<td>AR, 3q25</td>
<td>Deletions resulting in multiple carboxylase deficiency and impaired release of biotin from biocytin, the product of biotin-dependent carboxylase degradation</td>
</tr>
<tr>
<td>Late infantile and juvenile sphingolipidoses</td>
<td>Progressive ataxia plus seizures, psychomotor regression, spasticity, extrapyramidal features, supranuclear gaze palsies</td>
<td>AR</td>
<td>22q13.3-qter - Deficiency of arylsulfatase A/sphingolipid activator protein deficiency</td>
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<td></td>
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<td></td>
<td>14q31 - Deficiency of galactosyleramid beta-galactosidase deficiency</td>
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<td></td>
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<td></td>
<td>1q21 - Autosomal recessive with multiple mutant alleles, resulting in deficiency of beta-glucocerebrosidase</td>
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<td></td>
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<td></td>
<td>18q11-q12 - Abnormal uptake of cholesterol and defective esterification leading to abnormal cholesterol ester storage</td>
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<tr>
<td></td>
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<td></td>
<td>15q23-q24 - Defect in hexosaminidase A or of the G-M2 protein activator</td>
</tr>
<tr>
<td>L-2 Hydroxyglutaric acidemia</td>
<td>Chronic progressive ataxia</td>
<td>Unknown locus AR</td>
<td>Deficiency of hepatic hydroxyglutaric acid dehydrogenase</td>
</tr>
<tr>
<td>Carbohydrate-deficient glycoprotein syndrome</td>
<td>Progressive ataxia plus</td>
<td>AR, 6p13.3-p13.2</td>
<td>Mutations in gene for phosphomannomutase</td>
</tr>
<tr>
<td>Leukoencephalopathy with ataxia</td>
<td>Progressive ataxia, spasticity</td>
<td>AR, 3q27</td>
<td></td>
</tr>
<tr>
<td>Disorder</td>
<td>Phenotype</td>
<td>Inheritance</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------------------</td>
<td>----------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>vanishing white matter</td>
<td>optic atrophy, seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinic-semialdehyde dehydrogenase deficiency</td>
<td>Progressive ataxia plus</td>
<td>AR, 6p22</td>
<td>- Accumulation of 4-hydroxybutyric acid in plasma and urine</td>
</tr>
<tr>
<td>NARP syndrome</td>
<td>Progressive ataxia plus</td>
<td></td>
<td>- Maternal inheritance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Mitochondrial ATP-6 NARP 8993 mutation, causing base substitution T-to-G or T-to-C (AMA 370) at nucleotide position 8993</td>
</tr>
<tr>
<td>Leigh disease</td>
<td>Progressive ataxia plus lactic acidosis</td>
<td>AR/maternal inheritance</td>
<td>- Multiple biochemical and molecular defects underlying condition (e.g., PDH complex deficiency, cytochrome oxidase C deficiency, mitochondrial ATPase 6)</td>
</tr>
</tbody>
</table>

*AD - Autosomal dominant  
†AR - Autosomal recessive

**ATAXIA WITH PROGRESSIVE MYOCLONIC EPILEPSIES**

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.

- **Unverricht-Lundborg Disease**

Heinrich Unverricht (September 18, 1853 - April 22, 1912) was a German internist who was a native of Breslau. In 1877 he obtained his doctorate from the University of Breslau, where he was a student of Michael Anton Biermer (1827-1892). Later he was a professor at Jena (1886) and Dorpat (1888), where he resigned in 1892 for political reasons, and became director of the city hospital at Magdeburg-Sudenburg.

Heinrich Unverricht is most remembered for his research of epilepsy, especially his work with progressive myoclonus epilepsies (PME). In 1891 he described a form of PME that was later come to be known by the eponymous label "Unverricht-Lundborg disease". Equally notable, however, following Wagner (1863) and Virchow's (1866) initial clinical descriptions, in 1891 he developed the concept of an intimate connection between rash and muscle weakness that defined a new disorder: "...it seems to me that the skin appearance
plays such an important role in the disease picture that the designation Polymyositis is not completely accurate. In our case, the partnership of the skin and muscle disease allows us to use the elocution Dermatomyositis. Unverricht published over fifty medical works, including Studien über die Lungenentzündung, his prize-winning doctorate thesis on pneumonia.

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 subband 21q22.3. The gene CST6 codes for a protein called cystatin B, a noncaspase cysteine protease inhibitor. Cystatin B mRNA was reduced markedly in EPM1 patients. The mutation results from an unstable dodecamer repeat expansion in the promoter region of the CST6 gene.

Figure 13. **Heinrich Unverricht**

- **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 features**
  - EEG is 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.

**Lafora Body Disease**

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.

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**Figure 14. Lafora bodies**

- 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 features
• 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.

  o Treatment

The disorder is fatal. Symptomatic treatment for seizures and myoclonus may be tried.

  • Neuronal Ceroid Lipofuscinosis

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 of this enzyme have been demonstrated as deficient in CLN2 autopsy specimens.

  o Clinical features
    ▪ Ataxia
    ▪ Dementia
    ▪ Myoclonic seizures, atypical absence seizures, GTC seizures, other seizure types
    ▪ Visual impairment
  
  o Laboratory features
    ▪ CT scan and MRI show predominantly cerebellar atrophy.
    ▪ 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.
    ▪ The diagnosis can be suspected on the basis of abnormal driving responses on the EEG to photic stimulation (high-amplitude spike at low rates of stimulation).
- **Treatment**

The disorder is progressive and fatal. No treatment is available, although symptomatic treatment and supportive measures may help improve the quality of life.

**Figure 15.** Neuronal ceroid lipofuscinosis (NCL). (A) Axial T2-weighted MR image of patient with infantile NCL reveals dark, atrophied thalami (arrow), diffuse volume loss, ventriculomegaly, and significant delay in myelin maturation. (B) Axial T2-weighted image of patient with juvenile variant demonstrates atrophied thalami and loss of signal within the periventricular white matter and the posterior limb of internal capsule (arrow).

**Figure 16.** Magnetic resonance imaging study of the brain in a patient with neuronal ceroid lipofuscinosis showing cerebellar atrophy on sagittal view.
Myoclonic Epilepsy With Ragged Red Fibers

Myoclonic epilepsy with ragged red fibers (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\textsubscript{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 often photosensitive and exaggerated by voluntary movements

- **Laboratory features**
  - CT scan 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 is present.
  - Mutation analysis can be performed to demonstrate mtDNA mutation.

- **Treatment**
  - No specific treatment measures exist. Treat seizures symptomatically.
### Table 5. Progressive myoclonic Epilepsy

<table>
<thead>
<tr>
<th>Progressive Myoclonic Epilepsies</th>
<th>Neurologic Phenotype</th>
<th>Genetic-Biochemical Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unverricht-Lundborg syndrome</td>
<td>Myoclonus, ataxia, and seizures</td>
<td>AR*, 21q22.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mutations involving dodecamer repeat expansions affecting the gene for cystatin B</td>
</tr>
<tr>
<td>Lafora body disease</td>
<td>Myoclonus, ataxia, and seizures</td>
<td>AR, 6q24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mutation affecting gene for a protein tyrosine phosphatase (laforin), which may disrupt glycogen metabolism</td>
</tr>
<tr>
<td>MERRF</td>
<td>Myoclonus and ataxia</td>
<td>Maternal inheritance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- mtDNA mutations affecting tRNA&lt;sup&gt;Ly&lt;/sup&gt; defective oxidative phosphorylation</td>
</tr>
<tr>
<td>Late infantile neuronal ceroid lipofuscinosis</td>
<td>Myoclonus, ataxia, and seizures</td>
<td>AR, 11p15.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Gene coding for lysosomal pepstatin insensitive protease</td>
</tr>
</tbody>
</table>

*AR - Autosomal recessive

**CONCLUSIONS**

- Biochemical defects that affect myriad pathways can result in disorders with ataxia as the sole presentation or part of a more generalized syndrome.
- Most biochemical defects have a genetic basis, and both traditional mendelian and nontraditional inheritance mechanisms are involved.
- 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 in the evaluation (see Picture 1).

Many of these neurodegenerative conditions are progressive, with no treatment currently available. Other specific defects such as ataxia with selective vitamin deficiency are eminently treatable, and still others such as urea cycle defects may have treatment that prolongs life and reduces morbidity.

Advances in the field of molecular genetics have improved the understanding of these diseases. New techniques will guide the way for future therapeutic advances.

References