

Ataxic Disorders

Chapter 450 | Part 13: Neurologic Disorders

KEY CLINICAL POINTS

- 1 Symmetric ataxia suggests genetic, metabolic, immune, or toxic etiologies; focal ataxia implies a space-occupying lesion.
- 2 True cerebellar ataxia is distinguished from vestibular/labyrinthine disease by the absence of vertiginous complaints (dizziness, light-headedness).
- 3 Acute ataxias (hours/days) often involve intoxication (alcohol, lithium, phenytoin, barbiturates) or postinfectious syndromes.
- 4 Subacute ataxias (weeks/months) may result from vitamin B1/B12 deficiency, paraneoplastic syndromes, or environmental toxins.
- 5 Chronic ataxias (months/years) often point toward inherited diseases (SCAs, Friedreich's), metabolic disorders, or chronic infections.
- 6 SCA3 (Machado-Joseph Disease) is the most common autosomal dominant ataxia and presents in three distinct clinical types.
- 7 Friedreich's Ataxia is the most common inherited ataxia, caused by GAA triplet repeats in the frataxin gene leading to mitochondrial iron accumulation.
- 8 Ataxia Telangiectasia (AT) involves ATM gene mutations, defective DNA repair, and high risk for various cancers.
- 9 Omaveloxolone is the only FDA-approved agent for Friedreich's ataxia as an NFR2 agonist.
- 10 Prion disease treatment focuses on reducing PrPC levels to address the substrate for PrPSc.

DEFINITION & CLASSIFICATION

- **Clinical Presentation:** Characterized by gait impairment, scanning speech, visual blurring (nystagmus), hand incoordination, and tremor with movement.
- **Pathophysiology:** Result from involvement of the cerebellum and its afferent/efferent pathways (spinocerebellar and frontopontocerebral).
- **Distinction from Vestibular Disease:**

→ True cerebellar ataxia: No vertiginous complaints; characterized by unsteady gait due to imbalance.

→ Vestibular/Labyrinthine disease: Associated with significant dizziness, light-headedness, or perception of movement.

- **Symmetric Ataxia (Definition):** "A gradual and progressive increase in symptoms with bilateral and symmetric involvement suggests a genetic, metabolic, immune, or toxic etiology."
- **Focal Ataxia (Definition):** "Focal, unilateral symptoms with headache and impaired level of consciousness accompanied by ipsilateral cranial nerve palsies and contralateral weakness imply a space-occupying cerebellar lesion."
- **Classification by Onset:**

- Acute: Hours to days.
- Subacute: Weeks to months.
- Chronic: Months to years.

EPIDEMIOLOGY

- **Prevalence:** Ataxias with autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance are found worldwide.
 - **Common Types:** Machado-Joseph disease (SCA3) and Friedreich's ataxia are the most common types in most populations.
 - **Friedreich's Prevalence:** Composes one-half of all hereditary ataxias.
 - **Management Impact:** Genetic markers allow for precise diagnosis, family planning, and identification of asymptomatic preclinical disease.
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ETIOLOGY & PATHOPHYSIOLOGY

- **Prion Diseases:**

- Treatment strategy: Reduce PrPC (the substrate for PrPSc) rather than directly eliminating PrPSc.
- Rationale: Reduction of PrPC is independent of the specific pathogenic form of PrPSc and allows for normal lifespan in models.

- **Autosomal Dominant Ataxias (SCAs):**

- Mechanism: CAG triplet repeat expansions → expanded polyglutamine proteins (ataxins) → toxic gain of function.
- Toxicity factors: High expression, conformational change to β -pleated structure, abnormal nuclear transport, binding to other proteins (TATA-binding, CREB-binding), impaired ubiquitin-proteasome system, and induced apoptosis.
- Anticipation: Larger expansions lead to earlier age of onset and more aggressive disease in subsequent generations.

- **Friedreich's Ataxia:**

- Genetics: frataxin gene (9q13-q21.1) with expanded GAA triplet repeats (Normal: 7-22; Patients: 200-900).
- Pathophysiology: Loss of frataxin → mitochondrial iron accumulation → deficiency in iron/sulfur clusters → decreased ATP production → cellular injury.

- **Vitamin E Deficiency Syndromes:**

- Abetalipoproteinemia (Bassen-Kornzweig): MTP mutation → impaired VLDL formation → lack of vitamin E delivery to CNS.
- Ataxia with Vitamin E Deficiency (AVED): α -TTP mutation → inability to bind vitamin E to VLDL.

- **Ataxia Telangiectasia (AT):**

- Genetics: ATM gene (11q22-23) mutation → defective DNA repair.

→ Clinical features: Progressive telangiectatic lesions, nystagmus, truncal/limb ataxia, and high risk for lymphomas and other cancers.

- **Mitochondrial Ataxias:** Associated with various mutations in mitochondrial DNA (mtDNA).

CLINICAL FEATURES

- **SCA1:**

→ Genetics: ≥ 40 CAG repeats.

→ Clinical: Correlation between larger repeat number and younger age of onset; anticipation present.

- **SCA2 (MJD):**

→ Genetics: 60-84 CAG repeats.

→ Pathophysiology: Ataxin-3 forms aggregates, impairing proteasome function.

- **SCA3 (Machado-Joseph Disease):**

→ Type I (ALS-parkinsonism-dystonia): Early onset (<2 decades); weakness/spasticity; facial/lingual fasciculations; no truncal titubation.

→ Type II (Ataxic): 2nd to 4th decades; true cerebellar deficits (dysarthria, gait ataxia) plus corticospinal/extrapyramidal signs.

→ Type III (Ataxic-amyotrophic): 5th to 7th decades; pancerebellar disorder with peripheral neuropathy and absent reflexes.

- **SCA6:**

→ Genetics: 21-27 CAG repeats.

→ Note: Missense mutations may lead to familial hemiplegic migraine.

- **SCA7:**

→ Distinctive feature: Retinal pigmentary degeneration (blue-yellow color blindness) and macular degeneration.

- **SCA8:**

→ Genetics: CTG repeat expansion; marked maternal bias in transmission.

- **SCA27B:**

→ Genetics: Intronic GAA repeat in FGF14 gene; median onset 60 years; includes afferent sensory deficits and dysautonomia.

- **DRPLA:**

→ Genetics: ≥ 49 CAG repeats in atrophin gene; features include choreoathetosis, dystonia, seizures, and myoclonus.

DIFFERENTIAL DIAGNOSIS

- **Symmetric vs. Focal Ataxia:**

→ Symmetric: Suggests genetic, metabolic, immune, or toxic etiology.

→ Focal: Suggests space-occupying lesion (e.g., tumor, abscess, hemorrhage).

DIAGNOSTIC APPROACH

1. Assess Symmetry and Presentation:

- Symmetric → investigate metabolic, toxic, or genetic causes.
- Focal + Headache/Altered Consciousness → suspect space-occupying lesion (tumor, abscess, hemorrhage).

2. Determine Clinical Timeline (Table 450-1):

- Acute (Hours to Days) → Check for Intoxication (alcohol, lithium, phenytoin, barbiturates), Viral cerebellitis, or Postinfection syndrome.
- Subacute (Days to Weeks) → Check for Mercury/Solvents, Chemotherapy effects, Vitamin B1/B12 deficiency, Lyme disease, Paraneoplastic syndromes, Antigliadin antibody syndrome, Hypothyroidism, or Phenytoin/Amiodarone toxicity.
- Chronic (Months to Years) → Investigate Inherited diseases, Tabes dorsalis, Hypothyroidism, AIDS-related multifocal leukoencephalopathy, or Congenital lesions (Chiari/Dandy-Walker).

3. Imaging and Lab Work:

- MRI/CT: Identify mass lesions (Neoplastic/Infectious), vascular events, or structural malformations.
 - CSF Analysis: Support diagnosis of viral cerebellitis or MS.
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MANAGEMENT & TREATMENT

1. Address Underlying Cause:

- Intoxication → Remove offending agent (e.g., lithium, alcohol).
- Nutritional Deficiency → Supplement Vitamin B1 or B12.
- Hypothyroidism → Hormone replacement.

2. Specific Pharmacologic Treatments:

- Friedreich's Ataxia → Omaveloxolone (NRF2 agonist) to address mitochondrial dysfunction.
- SCA27B → 4-aminopyridine (improves episodic symptoms and severity of ataxia).

3. Genetic Counseling:

- Provide for inherited ataxias (SCA, Friedreich's, AT) to assist with family planning and identification of asymptomatic carriers.
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KEY PEARLS & HIGH-YIELD POINTS

- **Clinical Distinction:** True cerebellar ataxia is defined by the absence of vertiginous symptoms (dizziness/light-headedness).
 - **Symmetry Rule:** Symmetric progression points toward systemic/genetic issues; focal presentation points to local lesions.
 - **Prion Strategy:** Treatment focuses on reducing PrP^C levels as it is independent of the specific pathogenic PrP^{Sc} form.
 - **Friedreich's Pathophysiology:** Result of frataxin deficiency → iron accumulation in mitochondria → low ATP.
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REFERENCE TABLES

TABLE 450-1

Etiology of Cerebellar Ataxia

SYMMETRIC AND PROGRESSIVE SIGNS			FOCAL AND IPSILATERAL CEREBELLAR SIGNS		
ACUTE (HOURS TO DAYS)	SUBACUTE (DAYS TO WEEKS)	CHRONIC (MONTHS TO YEARS)	ACUTE (HOURS TO DAYS)	SUBACUTE (DAYS TO WEEKS)	CHRONIC (MONTHS TO YEARS)
Intoxication: alcohol, lithium, phenytoin, barbiturates (positive history and toxicology screen) Acute viral cerebellitis (CSF supportive of acute viral infection) Postinfection syndrome	Intoxication: mercury, solvents, gasoline, glue Cytotoxic chemotherapeutic drugs Alcoholic-nutritional (vitamin B ₁ and B ₁₂ deficiency) Lyme disease	Paraneoplastic syndrome Antigliadin antibody syndrome Hypothyroidism Inherited diseases Tabes dorsalis (tertiary syphilis) Phenytoin toxicity Amiodarone	Vascular: cerebellar infarction, hemorrhage, or subdural hematoma Infectious: cerebellar abscess (mass lesion on MRI/CT, history in support of lesion)	Neoplastic: cerebellar glioma or metastatic tumor (positive for neoplasm on MRI/CT) Demyelinating: multiple sclerosis (history, CSF, and MRI are consistent) AIDS-related multifocal leukoencephalopathy (positive HIV test and CD4 ⁺ cell count for AIDS)	Stable gliosis secondary to vascular lesion or demyelinating plaque (stable lesion on MRI/CT older than several months) Congenital lesion: Chiari or Dandy-Walker malformations (malformation noted on MRI/CT)