Ataxia

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KEYWORDS

• Ataxia • Inherited • Sporadic • Autosomal dominant • Autosomal recessive
• Mitochondrial • Diagnosis • Treatment

KEY POINTS

- Balance and coordination are products of complex circuitry involving the basal ganglia, cerebellum, and cerebral cortex, as well as peripheral motor and sensory pathways.
- Malfunction of any part of this intricate circuitry can lead to imbalance and incoordination, or ataxia, of gait, the limbs, or eyes, or a combination thereof.
- Ataxia can be a symptom of a multisystemic disorder, or it can manifest as the major component of a disease process.
- Ongoing discoveries of genetic abnormalities suggest the role of mitochondrial dysfunction, oxidative stress, abnormal mechanisms of DNA repair, possible protein misfolding, and abnormalities in cytoskeletal proteins.
- Few ataxias are fully treatable, and most are symptomatically managed.

INTRODUCTION

Complex circuitry connecting the basal ganglia, cerebellum, and cerebral cortex is involved in producing coordinated movements of the eyes and limbs. Malfunction of any part of this intricate circuitry can lead to incoordination, or ataxia, of gait, the limbs, or eyes, or a combination thereof. Afferent inputs into the motor circuitry are also critical in production of coordinated movements, and disruptions in sensory pathways can produce incoordination known as sensory ataxia. Ataxia can be acquired, inherited, or sporadic (lacking a definite genetic defect or acquired etiology). This review focuses on the inherited ataxias, their clinical presentation, pathophysiology, and available treatments, with a quick overview of acquired ataxias.

ACQUIRED ATAXIAS

Vascular insults, including strokes and global anoxic events, tumors, trauma, and demyelinating disease (ie, multiple sclerosis) are common causes of acquired ataxia.

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Other causes include congenital anomalies, infection, autoimmunity, and vitamin deficiencies. Detailed history and examination, imaging studies, and other corroborating tests often confirm the etiology in these cases. Hypothyroidism can occasionally cause mild disequilibrium and gait ataxia with pathology in the midline cerebellar structures.[1] Symptoms can be dramatically improved with timely recognition and thyroid replacement.[2] Alcohol is a major toxic cause of ataxia and excessive use leads to degeneration of the midline cerebellum. Progressive trunk and gait ataxia is characteristic, with little involvement of upper limbs, eyes, or speech (a corollary of relative cerebellar hemispheric sparing). More than 1 year of abstinence can improve ataxia drastically.[3] Chemotherapy agents, especially 5-fluorouracil and cytosine arabinoside, can cause a cerebellar syndrome, particularly when given in higher than conventional doses.[4] Supratherapeutic serum levels of antiepilepsy drugs, particularly phenytoin, are associated with acute reversible dose-dependent cerebellar signs, and permanent ataxia may emerge with chronic use. All but 2 antiepilepsy drugs (gabapentin and levetiracetam) were shown in a meta-analysis to have a higher and dose-dependent risk of imbalance.[5] Heavy metals can also cause ataxia. Paresthesias, ataxia, and visual field defect can be seen in organic mercury exposure. Lead poisoning, particularly in children, is typically associated with encephalopathy and abdominal colic, but ataxia can be a prominent presenting feature. Chelation therapy has been reported to successfully restore neurologic function.[6] Excessive use of bismuth subsalicylate (eg, Pepto-Bismol) can cause bismuth toxicity, which is associated with ataxic gait, myoclonus, and confusion.[7] Abuse of paint products that contain toluene may lead to persistent ataxia, cognitive impairment, and pyramidal tract signs.[8]

Ataxia can be caused by infectious or postinfectious syndromes involving the cerebellum, brainstem, or both. Neuroimaging, serology, and cerebrospinal fluid analysis can help to identify the etiology. Combination of ophthalmoplegia, ataxia, and other cranial nerve deficits is suggestive of Bickerstaff encephalitis.[9] Ataxia can be one of many neurologic symptoms in human immunodeficiency virus infection. Rapidly progressive ataxia and dementia can be seen in Creutzfeldt–Jakob disease. Ataxia is a more common neurologic symptom of Whipple's disease than the pathognomonic feature of oculomasticatory myorhythmia.[10] The condition, which is otherwise fatal, should be promptly diagnosed using brain imaging, cerebrospinal fluid assays, and duodenal biopsies, and treated with antibiotics.[10]

Paraneoplastic cerebellar degeneration is one of several autoimmune causes of ataxia, and can be associated with other neurologic signs, including dysarthria, oscillopsia, dementia, and extrapyramidal signs.[11] Thorough neoplasia workup should be performed, because cancer treatment can improve the ataxia. Anti-Purkinje cell antibodies, such as anti-Yo, Hu, and Ri antibodies, may be detectable. The combination of ataxia, hyperreflexia, and peripheral neuropathy is seen in celiac disease owing to gluten sensitivity. Dietary restriction of gluten can improve symptoms once the diagnosis is confirmed with antibody testing and small bowel biopsy.[12]

Anti-Glutamic Acid Decarboxylase Ataxia

Antibodies against glutamic acid decarboxylase have been reported in patients with progressive ataxia.[13] The affected are typically adult women who present with ataxia, nystagmus, and dysarthria, and develop antibodies against thyroid, parietal cells, and pancreatic islet cells, the latter leading to insulin-dependent diabetes. Glutamic acid decarboxylase is instrumental in synthesizing gamma-aminobutyric acid from glutamate, and the antibodies are thought to pathologically bind to