Overview of Adult Onset Cerebellar Ataxia

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The ataxias are clinically heterogenous disorders caused by pathological processes affecting the cerebellum and cerebellar pathways resulting in impaired coordination. The cerebellum’s main function is to integrate information relayed to it and facilitate the execution of precise movements. Lesions of the cerebellum and its connections can result in breakdown and incoordination of movement.

WHAT PROCESSES CAN CAUSE ATAXIA?
The pathophysiology of cerebellar ataxias is as diverse as the various neurological and systemic diseases affecting the cerebellum. Broadly classifying ataxias into genetic and non-genetic conditions is a first step in discovering their underlying mechanism. Non-genetic ataxias are caused by acquired conditions, sporadic neurodegenerative disorders, or from unknown processes in which case the descriptive term idiopathic late-onset cerebellar ataxia (ILOCA) is used to describe the disorder.

WHAT ARE COMMON CEREBELLAR SYMPTOMS?
Difficulties with gait and balance are the most common symptoms, often described as “losing balance,” “staggering,” “walking like a drunk,” “cannot walk a straight line,” etc. Other complaints include dizziness, blurred vision, slurred speech, difficulty with swallowing, clumsiness, sloppy handwriting, poor fine motor skills, and tremor.

WHAT IS INVOLVED IN THE EVALUATION OF AN ATAXIC PATIENT?
As with all neurological disorders, a detailed history and thorough examination are prerequisites for an accurate diagnosis and set the stage for the diagnostic investigation. Motor and non-motor symptoms, family history, acquired risk factors (exposure to toxins and certain general medical conditions), and tempo of progression are key elements of the history.

Cerebellar symptoms (see above) point to an ataxic disorder, while some non-cerebellar symptoms are more tightly correlated with disease than others. For example:
- Postural dizziness, erectile dysfunction, urinary symptoms, and dream-enactment behavior (suspicious for Rapid eye movement behavior disorder or REMBD): Multiple System Atrophy-C (MSA-C)
- Profound cognitive and behavioral changes: sporadic Creutzfeldt-Jakob disease (CJD); paraneoplastic, infectious, and immune-mediated limbic encephalitides

Other neurological symptoms, when corroborated by examination findings, may help with the diagnosis.

Family history of ataxia, when present, is very helpful for diagnosis of genetic ataxias. However, when the family history is absent or unknown, this does not exclude a genetic cause. Usual patterns of inheritance are autosomal dominant (AD) or recessive (AR) and X-linked. Consanguinity between parents should alert to an autosomal recessive disorder.

Common risk factors for cerebellar damage include:
- Frequent and excessive alcohol consumption; exposure to toxins such as mercury; use of medications like phenytoin, lithium, and chemotherapeutic agents
- HIV, hepatic cirrhosis, multiple sclerosis (MS), and autoimmune diseases
- Gastric-bypass procedures and malabsorption states causing deficiency of vitamins E and B1.

WHAT DOES VARIABILITY IN RATE OR PROGRESSION INDICATE?
Rate of progression of ataxic symptoms can be associated with specific causes of ataxia.

Acute and abrupt onset is associated with strokes and structural brain lesions. Rapid progression in hours or days is associated with infectious or parainfectious cerebellitis; immune-mediated disorders such as Miller-Fisher syndrome (MF); acute toxin exposure; rapid metabolic derangement; or multiple sclerosis (MS).

Progression over weeks to months is associated with paraneoplastic disorders; anti-glutamic acid decarboxylase (GAD)-antibody syndrome; steroidresponsive encephalopa-
thy and ataxia (SREAT or Hashimoto’s encephalopathy); gluten ataxia in Celiac disease (GA); vitamin deficiency states (e.g., ataxia with vitamin E deficiency or AVED, B1 (thiamine) deficiency); general medical conditions such as hepatic encephalopathy; infections (HIV, CJD); MS; or sensory polyneuropathy and ganglionopathy (SPN and SG).

Chronic and indolent progression over months to years is most frequently associated with genetic ataxias; toxins (primarily alcohol); MS; storage disorders (lipid, lysosomal, peroxisomal); sporadic neurodegenerative disorders (MSA-C); ILOCA; SPN and SG; atypical parkinsonian conditions, such as Progressive supranuclear palsy (PSP); or Neurosyphilis (NS).

Rates of progression vary in individuals. All possible etiologies should be considered when the clinical course is not firmly established. These include:

- **Cerebellar signs**: Nystagmus, saccadic dysmetria, impaired cancellation of vestibulo-ocular reflex, dystarthria, limb ataxia, titubation, dysmetria, impaired check on rebound testing, end-intention tremor, wide stance, and difficulty with tandem stance and gait.
- **Extracerebellar signs and related diseases**: Orthostatic hypotension, dysphonia, dystonia, pyramidal signs, and parkinsonism: MSA-C (the most common non-genetic degenerative ataxia).
- **Dystonia, Parkinsonism**: Several SCAs; DRPLA; Wilson’s disease and Neuroacanthocytosis (NAC) in a younger cohort.
- **Action tremor, dysexecutive syndrome, neuropathy, Parkinsonism**: Fragile-X tremor ataxia syndrome (FXTAS).
- **Chorea**: Huntington disease, HD; dentatorubropallidoluysian atrophy, DRPLA; SCA 17; Ataxia telangiectasia, AT; SCAs.
- **Myoclonus and cognitive impairment**: hepatic encephalopathy; CJD; anti-GAD syndrome; POLG (polymerase γ) mutation.
- **Pyramidal signs, sensory loss**: Strokes; acquired and genetic myelopathies; hereditary spastic parapareses; spinocerebellar ataxias (SCAs); Friedreich’s ataxia (FA); MS; NS.
- **Sensory loss, hyporeflexia**: AR ataxias; SPN and SG (“sensory ataxia”); GA; MF; AVED; NS.
- **Cognitive and psychiatric symptoms**: CJD; Wernicke-Korsakoff syndrome; SCA 17; late-stage AD ataxias; AR adult-onset inborn errors of metabolism; leukodystrophies; NS; Whipple’s disease.
- **Eye-movement abnormalities**: MS; ataxias with oculomotor apraxia 1 and 2 (AOA1, AOA2); SCA 2; Whipple’s disease; Ataxia telangiectasia, AT; MF; PSP (impaired vertical saccades).
- **Visual loss**: MS; ataxia with vitamin E deficiency (AVED); SCA7; mitochondrial disorders.
- **Neuromuscular deficits**: mitochondrial disorders.
- **Telangiectasias**: AT.
- **Achilles xanthomas and early cataracts**: Cerebrotendinous xanthomatosis, CTX.

**WHAT DIAGNOSTIC TESTS ARE RECOMMENDED FOR ATAXIA EVALUATION?**

Brain MRI is indispensable. It may reveal:

- Structural lesions and strokes.
- Atrophy of the cerebellum and brainstem: chronic processes such as genetic ataxias.
- Abnormal signal and atrophy of the basal ganglia: Wilson’s disease; HD; mitochondrial disorders; NAC.
- Putaminal atrophy and cruciform hyperintensity in the pons (“hot-cross bun” sign): MSA-C.
- Middle cerebellar peduncle lesions: FXTAS.
- White matter abnormalities: MS; adult-onset leukodystrophies (Alexander disease, AD; Adrenoleukodystrophy, ALD).
- Diffusion-weighted abnormalities (“cortical ribboning”) and symmetric thalamic changes (“pulvinar” sign): CJD
- Spinal cord MRI is suggested for myelopathic signs.
- Severe cord atrophy: FA; Alexander disease

Additionally, serum testing may be indicated and is guided by the clinical evaluation and imaging:

- First tier: blood chemistries; renal and liver function tests; ammonia; complete blood counts with differential (CBC diff); erythrocyte sedimentation rates (ESR); Antinuclear antibodies (ANA); thyroid and vitamin levels (B12, B1, E, B6, A); folate; glucose tolerance test; methylmalonic acid; infectious serologies (HIV antibody, Lyme antibody, RPR); Serum protein electrophoresis with immunofixation (SPEP with IFE).
- Second tier (tests for rare ataxias and potentially treatable conditions, to be ordered if 1st tier testing is inconclusive): creatine kinase; lactate; pyruvate; α-fetoprotein (elevated in AT and AOA 2); fasting lipid profile; paraneoplastic antibodies (Hu, Yo, Ri, Ma, TA, CARP8, CV2, Tr, LEMS, MGLUR1, CRMP5, GQ1b, amphiphysin, PCA-2, NMDA, VGKC, ganglionic acetylcholine receptor antibodies); anti GAD65 antibodies; SSA, SSB antibodies (Sjögren’s antibodies); antigliadin antibodies (IgA and IgG); serum iron studies; alkaline phosphatase; thyroid peroxidase (TPO) antibodies; 24 hour urine copper and zinc; serum copper and ceruloplasmin; urine heavy metals; Human T-Cell lymphotropic virus I, II; T. Whipplei PCR; cholesterol levels (if CTX is suspected).
- Third tier (rarer genetic conditions typically seen in a younger cohort with ataxia and other symptoms such as}
as dystonia, peripheral neuropathy, visceral involvement and cognitive impairment; peripheral blood smear for acanthocytes (for NAC); lysosomal screen; plasma amino acids; urine organic acids; serum ketones; fasting very long chain fatty acids (for ALD).

Cerebrospinal fluid studies are obtained for paraneoplastic, immune-mediated, infectious, and inflammatory disorders: protein; glucose; CBC cliff; cultures; IgG synthesis, index, rate; oligoclonal bands; cytology; lactate; 14-3-3 protein; paraneoplastic antibodies; viral encephalitis panel; VDRL.

CT or PET scan of the body may be indicated to look for occult malignancy. Additional tests that may be helpful in certain settings include EEG (helpful in CJD), Electromyogram and nerve conduction studies, autonomic studies, or sleep study (to look for REMBD). Rarely, nerve and muscle biopsies are used for suspected mitochondrial ataxias or brain biopsy for suspected leukodystrophies. Other rarely indicated tests include magnetic resonance spectroscopy of the brain, dopamine transporter SPECT (DaT) scan (abnormal in MSA-C), or genetic tests.

The literature offers a detailed discussion of genetic ataxias.

The patient should be appropriately counseled about the implications and costs of genetic testing before it is ordered. Testing may reveal:

- AD mutations: SCAs (most common worldwide is SCA 3 or Machado-Joseph disease), DRPLA, and the rare episodic ataxias (EA 1, EA 2).
- AR mutations: have usual age of onset <20 years but later onset FA, AT, AOA 2 have been reported; POLG mutations.
- X-linked mutation (premutation in the FMR1 gene): FXTAS.
- Mitochondrial DNA mutations.

Specialized gene tests for inborn errors of metabolism, leukodystrophies, and storage disorders should be ordered if the rest of the evaluation raises suspicion for these rare conditions.

WHAT IF NO CAUSE IS IDENTIFIED AFTER EXTENSIVE TESTING?

A large number of sporadic ataxias do not seem to have an identifiable etiology. When followed over time about one-third of ILOCAs may evolve to MSA-C. Unidentified genetic mutations may account for the rest of these ataxias.

HOW ARE ATAXIAS TREATED?

Specific interventions for acquired ataxias include steroids and other immunomodulating therapies for SREAT, paraneoplastic disorders, and other immunological disorders. When an underlying malignancy is detected, it must be treated. Gluten-free diets are indicated for GA. Specific pharmacologic agents include acetazolamide is used for EA2, SCA 6 and varenicline (Chantix®) for SCA 3. Bile acid replacement may be tried for CTX. Common sense measures include elimination of toxins; correction of deficiency states; and, treatment of medical disorders causing ataxia.

Non-specific pharmacological agents of potential benefit include amantadine, alpha-lipoic acid, buspiroone, branched-chain amino acids, creatine, coenzyme Q10, vitamin E, physostigmine,riluzole, and selective serotonin reuptake inhibitors. Cerebellar tremor may improve with primidone and antiepileptics; oscillopsia with memantine and GABA agonists; and spasticity with central anti-spasticity drugs.

A multidisciplinary approach is necessary in MSA-C, due a multitude of progressive motor and non-motor symptoms. Rehabilitative therapies should be offered to all patients with ataxia. Continuous exercise programs have shown positive results.

SUMMARY

The diagnostic approach to adult onset ataxias should be systematic and guided by the history and examination. Non-genetic ataxias may involve an extensive and expensive evaluation that may be done in a tiered fashion. MSA-C is the most common sporadic ataxia. ILOCA is a diagnosis of exclusion. A positive familial history signals a genetic disorder.

Patients undergoing genetic tests should be appropriately counseled. Effective management of ataxic disorders requires a multidisciplinary approach involving disease-specific and symptomatic drug treatment as well as rehabilitative measures.

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