Evaluation
and
Management
of

Ataxic Disorders

AN OVERVIEW
FOR PHYSICIANS

Susan L. Perlman, MD
for the
National Ataxia Foundation

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EVALUATION AND MANAGEMENT OF ATAXIC DISORDERS
An Overview for Physicians

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Printed in the United States of America

ISBN: 0-943218-14-4

Library of Congress Control Number: 2007923539

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Acknowledgements

This booklet was made possible through the immeasurable dedication of Susan Perlman, MD. Dr. Perlman has been a tremendous asset to the National Ataxia Foundation and to those affected by ataxia. Dr. Perlman's commitment to ataxia is extraordinary, and she took time out of a very busy schedule to write this handbook.

The National Ataxia Foundation would like to extend a special thank you to Dr. Susan Perlman for her time and commitment in writing this handbook.

Preface

This book is intended to inform and guide family practice and other physicians who may be caring for patients with ataxic symptoms or who have been diagnosed with ataxia.

The goals of this book are threefold:

1) To provide health care practitioners with a vocabulary to aid in their understanding of what is and is not ataxia.

2) To provide diagnostic protocols for use in defining the types and causes of ataxia that are seen in medical practice.

3) To provide resources for use in counseling and managing the ataxic patient.

There is nothing more discouraging for a patient or family member than to be given a specific diagnosis, and then be told that "there is nothing that can be done." Physicians are equally disheartened to see exponential progress in the understanding of the pathophysiology of complex disorders, but little being made available that will yield direct benefits for the treatment of their patients. Over the past 20 years, molecular genetic research has completely revolutionized the way the progressive cerebellar ataxias are classified and diagnosed, but has yet to produce effective gene-based, neuroprotective, or neurorestorative therapies. We are fortunate that in the past five years, several pharmaceutical companies, partnering with research groups, have begun to add drugs to their pipelines that may have application to cerebellar ataxia in the near future.

The current treatment of cerebellar ataxia remains primarily a neurorehabilitation challenge (physical, occupational, and speech/swallowing therapy; adaptive equipment; driver safety training; nutritional counseling; psychosocial counseling), with modest additional gains made with the use of symptomatic medications.

Even in a situation where there really appears to be nothing else to offer, sharing of information and seeking new information together can provide strength and encouragement to the patient and family, which is the true foundation of the therapeutic relationship.

Thank you to my patients and their families for their willingness to work with me and to share with me their ideas and hopes.

Introduction

Ataxia is incoordination or clumsiness of movement that is not the result of muscle weakness. It is caused by cerebellar, vestibular, or proprioceptive sensory (large fiber/posterior column) dysfunction. Cerebellar ataxia is produced by lesions of the cerebellum or its afferent or efferent connections in the cerebellar peduncles, red nucleus, pons, medulla, or spinal cord. A unilateral cerebellar lesion causes ipsilateral cerebellar ataxia. Crossed connections between the frontal cerebral cortex and the cerebellum may allow unilateral frontal disease to mimic a contralateral cerebellar lesion.

Evaluation of the Ataxic Patient

Characteristics of ataxia

Cerebellar ataxia causes irregularities in the rate, rhythm, amplitude, and force of voluntary movements, especially at initiation and termination of motion, resulting in irregular trajectories (*dysynergia*), *terminal tremor*, and overshoot (*dysmetria*) in limbs. Speech can become dysrhythmic (*scanning dysarthria*) and articulation slurred, with irregular breath control. Difficulty swallowing or frank choking also may be present. Similar changes can be seen in control of eye movement, with jerky (saccadic) pursuit, gaze-evoked *nystagmus*, and *ocular overshoot/dysmetria*. Muscles show decreased tone, resulting in defective posture maintenance and reduced ability to check excessive movement (*rebound or sway*). Trunkal movement is unsteady, feet are held on a *wider base* during standing and walking, with *veering or drunken gait*, and the ability to stand on one foot or with feet together or to walk a straight line is diminished. Altered cerebellar connections to brainstem oculomotor and vestibular nuclei may result in sensations of "*dizziness*" or environmental movement (*oscillopsia*).

Vestibular ataxia has prominent *vertigo* (directional spinning sensations) and may cause past-pointing of limb movements, but spares speech.

Sensory ataxia has no vertigo or dizziness, also spares speech, worsens when the eyes are closed (*positive Romberg sign*), and is accompanied by *decreased vibration and joint position sense.*

Cerebellar influence is ipsilateral (the right cerebellar hemisphere controls the right side of the body), and within the cerebellum are regions responsible for particular functions. The midline cerebellum controls gait, head and trunk stability, and eye movements. The cerebellar hemispheres control limb tone and coordination, eye movements, and speech. Cerebellar signs on the neurologic exam can help to determine whether a process is unilateral or involves the entire cerebellum, and whether a particular region of the cerebellum has been targeted (vermis, outflow tracts, flocculonodular lobe, etc.). Certain etiologies may then become more likely.

The **genetically mediated ataxias** typically have insidious onset and relatively slow (months to years), symmetrical progression—affecting both sides of the body and moving from the legs to the arms to speech, or from midline (gait/trunk) to hemispheric (limb) structures, and ultimately to deep outflow pathways (increasing the component of tremor). **Acquired ataxias** may have more sudden or subacute onset and progression (weeks to months) and be asymmetrical or frankly focal in presentation. Acute onset with no progression suggests a monophasic insult (injury, stroke, hemorrhage, anoxia). Subacute onset with progression suggests infectious/inflammatory/immune processes, metabolic or toxic derangements, or neoplastic/mass effects.

Basic ataxia phenotypes

There are seven basic phenotypes:

- **Autosomal dominant cerebellar ataxia/spinocerebellar ataxia (SCA)**
- **Friedreich's ataxia-like syndromes**
- **Early onset cerebellar ataxia (EOCA)**
- **Mitochondrial syndromes**
- **Multiple system atrophy picture**
- **Idiopathic late onset cerebellar syndromes**
- **Hereditary spastic paraplegia/ataxia** (not discussed in this booklet)

Evaluation

The **neurological history** may provide clues to cause relating to associated illnesses, medication use, or lifestyle/environmental exposures (*see Table 1*). The **neurological examination** can be supplemented by **neural imaging** (magnetic resonance scanning/MRI or computed tomography/CT of the brain or spine) and **electrophysiologic studies** (electromyogram and nerve conduction/EMG-NCV; evoked potential testing—visual/VER, brainstem/

Table 1. IDENTIFIABLE CAUSES OF NONGENETIC ATAXIA

Type	Cause
Congenital	Developmental
Mass lesion of a specific type	Tumor, cyst, aneurysm, hematoma, abscess, normal pressure or partial obstructive hydrocephalus
Vascular	Stroke, hemorrhage; subcortical vascular disease
I**nfectious/Post-infectious/ Post-vaccination**	Anthrax; Epstein-Barr; enterovirus; HIV; HTLV; prion disease; Lyme disease; syphilis; measles, rubella, varicella; Whipple's disease; progressive multifocal leukoencephalopathy
Post-anoxic, post-hyperthermic, post-traumatic	
Chronic epilepsy	
Metabolic	Acute thiamine (B1) deficiency; chronic vitamin B12 and E deficiencies; autoimmune thyroiditis and low thyroid levels
Toxic *Drug reactions*	Amiodarone, cytosine arabinoside, 5-fluorouracil, lithium, phenytoin, valproic acid, and others
Environmental	Acrylamide, alcohol, organic solvents, organo-lead/mercury/tin, inorganic bismuth/ mercury/thallium
Immune-mediated *Vasculitis Paraneoplastic*[a]	Behcet's, giant cell arteritis, lupus, and others
Other autoantibodies	Anti-Yo, Hu, Ri, MaTa, CV2, Zic4; anti-calcium channel; anti-CRMP-5, ANNA-1,2,3, mGluR1, TR
Anti-immune therapies used in reported cases of immune-mediated cerebellar ataxia	Anti-GluR2, GAD[b], MPP1, GQ1b ganglioside; anti-gliadin (most common–reported also in the inherited syndromes as a possible secondary factor; treated with gluten-free diet)[c-e]
	Steroids, plasmapheresis, IVIG, rituximab, mycophenolatemofetil, methotrexate, and others

[a] Bataller, L., and J. Dalmau. Paraneoplastic neurologic syndromes: approaches to diagnosis and treatment. Semin Neurol, 2003 **23**(2): p. 215-24.

[b] Mitoma, H., et al. Presynaptic impairment of cerebellar inhibitory synapses by an autoantibody to glutamate decarboxylase. J Neurol Sci, 2000. **175**(1): p. 40-44.

[c] Bushara, K.O., et al. Gluten sensitivity in sporadic and hereditary cerebellar ataxia. Ann Neurol, 2001. **49**(4): p. 540-43

[d] Hadjivassiliou, M. et al. Dietary treatment of gluten ataxia. J Neurol Neurosurg Psychiatry, 2003. **74**(9): p. 1221-24

[e] Hadjivassiliou, M. et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. Brain, 2003. **126**(Pt 3): p. 685-91.

BAER, somatosensory/SSER; electronystagmography of oculomotor and vestibular pathways/ENG; electroencephalogram/EEG).

These can confirm the anatomic localization of the process and often the actual etiology (mass lesion of a specific type—e.g. tumor, cyst, hematoma, abscess; stroke or hemorrhage; subcortical vascular disease; inflammation/infection or vasculitis; demyelination; characteristic regional atrophy, hypo- or hyperintensities; normal pressure or partial obstructive hydrocephalus). **Additional laboratory** studies can then be ordered (blood; urine; spinal fluid; biopsy of muscle, nerve, or brain). There may be **key features on examination** that will provide clues to a specific cause for the ataxia *(see Table 2)*.

The presence of a known genetic disorder does not rule out the presence of additional acquired insults that might alter the presentation and course of the symptoms of ataxia and warrant independent investigation.

Similarly, the absence of a clear family history does not rule out the role of genetic factors in an apparently sporadic disorder. There may be no family history because the history wasn't taken, because the information is unavailable (adoption, loss of contact, noncooperation, paternity issues), because of nondominant inheritance patterns (recessive, X-linked, maternal/mitochondrial), or because of specific genetic processes that modify disease presentation in the pedigree (anticipation, incomplete penetrance, mosaicism).

Table 2. KEY FEATURES OF EXAMINATION THAT MAY PROVIDE CLUES TO THE DIAGNOSIS OF ATAXIA

Type	Features
Neurological Features	Ataxia with parkinsonism and autonomic dysfunction suggest multiple system atrophy (MSA)
	Accompanying dementia, seizures, ophthalmoplegia, or chorea suggest something other than MSA
Non-neurologic features	Cardiac (examples: cardiomyopathy, conduction disturbances) – Friedreich's ataxia (FRDA), mitochondrial disease
	Skeletal (examples: scoliosis, foot deformities) – FRDA, ataxia-telangiectasia, variants of Charcot-Marie-Tooth disease, late-on set inborn errors of metabolism
	Endocrine – diabetes (FRDA/mitochondrial, Wilson's disease), adrenalin sufficiency (adrenoleukodystrophy, or ALD; adrenomyeloneuropathy, or AMN)
	Liver/metabolic – inborn errors of metabolism
	Skin–phakomatoses (neurofibromatosis), ataxia-telangiectasia, inborn errors (vitamin E deficiency, sialidosis, ALD/AMN, Hartnup's, cerebrotendinous xanthomatosis [CTX])
Mitochondrial disorders seem to have more features beyond ataxia than do the other ataxic illnesses	Distinctive neurologic features: dementia, dystonia, exercise intolerance, hearing loss, migraine myelopathy, myoclonus, myopathy, neuropathy, ophthalmoplegia, optic neuropathy, pigmentary retinopathy, seizures, stroke-like episodes
	Distinctive non-neurologic features: adrenal dysfunction, anemia, cardiomyopathy, cataracts, diabetes mellitus, other endocrine dysfunction, exocrine pancreas dysfunction, intestinal pseudo- obstruction, lactic acidosis, renal disease, rhabdomyalysis, short stature

Genetic studies of large groups of patients with sporadic ataxia have shown from 4-29 percent to have one of the triplet repeat disorders (SCA6 most common), and 2-11 percent to have Friedreich's ataxia (FRDA)[1-3].

An interesting newly identified form of genetic ataxia is the fragile X-associated tremor/ataxia syndrome (FXTAS), typically occurring in the maternal grandfathers of children with fragile X mental retardation. It occurs without a family history of others with ataxia and can be misdiagnosed as Parkinson's disease or essential tremor because of the age of onset and the accompanying tremor. Affected persons with FXTAS also may have associated cognitive problems, which can be mistaken for Alzheimer's disease or a senile dementia[4-7]. Female carriers can be symptomatic.

Table 3 is a list of laboratory studies that can be performed on any ataxic patient, with or without a family history of ataxia, to help define the ataxia phenotype and to look for associated features and acquired causes. (In the older ataxic patient, multifactorial causes are more likely to occur, for example, vision problems plus vestibular issues plus vascular disease plus peripheral neuropathy.)

Table 3. WORKUP FOR THE ATAXIC PATIENT WITH OR WITHOUT A FAMILY HISTORY

- **MRI brain and spinal cord,** with and without contrast, with diffusion-weighted imaging (DWI) sequences
- **Electroencephalogram**
- **Evoked potentials** (visual, auditory, somatosensory)
- **Electronystagmogram** with caloric testing
- **Electromyogram** with nerve conduction studies
- **Chest X-ray**
- **1st line blood and urine studies**–CBC, chemistry panel, HgbA1c, fasting lipids, ESR, ANA, RPR, TSH, vitamin E, folic acid, vitamin B12, methylmalonic acid, homocysteine, urine heavy metals
- **2nd line blood and urine studies** – CPK, SPEP, post-prandial lactate-pyruvate-ammonia, ketones, copper, ceruloplasmin, zinc, ACE, Lyme titers, HTLV I/II, HIV, anti-thyroid antibodies, anti-gliadin antibodies (and anti-endomysial/anti-transglutaminase antibodies), anti-GAD antibodies (and antiamphiphysin antibodies)
- **3rd line blood and urine studies**– very long chain fatty acids/phytanic acid, plasma or urine amino acids, urine organic acids, lysosomal hydrolase screen including hexosaminidase A, coenzyme Q10 levels, glutathione levels, PRNP gene analysis
- **Spinal fluid studies** – cell count, glucose, lactate, protein, VDRL, gram stain, cultures as appropriate, cryptococcal antigen, 14-3-3 protein, neuron specific enolase, prion protein studies, neurotransmitter levels as appropriate, myelin basic protein, oligoclonal bands, IgG synthesis (process-specific), PCR (pathogen-specific)
- **Additional imaging**
  1. **MR spectroscopy**
  2. **PET scan/dopa-PET scan**
- **Biopsies** – conjunctival, muscle/nerve, GI tract, bone marrow, brain
- **Paraneoplastic workup** – appropriate imaging (ultrasound, CT, MRI), alpha fetoprotein, paraneoplastic antibodies (Yo, Hu, Ri, CV2, MaTa, Zic4, and others as available)
- **Genetic workup in the ataxic patient with no family history of ataxia** – in the patient over 50, occasionally positive gene tests for SCA6, SCA3, SCA1, Friedreich ataxia, and fragile X-associated tremor/ataxia syndrome (FXTAS) may be seen. Inborn errors of metabolism may occur in the patient over age 25[a]. Clinical whole exome sequencing can be considered.

[a] Gray, R. G., et al. Inborn errors of metabolism as a cause of neurological disease in adults: an approach to investigation. J Neurolo Neurosurg Psychiatry, 2000. **69**(1): p. 5-12.

Autosomal dominant cerebellar ataxia

The dominantly inherited ataxic disorders have an incidence of 1-5 in 100,000. They include the typical spinocerebellar ataxias (SCAs), which now number 40; the episodic ataxias (EA 1-8); and the atypical spinocerebellar ataxias (dentatorubral-pallidoluysian atrophy/DRPLA and Gerstmann-Straussler-Scheinker/GSS disease), which may have prominent features other than ataxia. Pathogenetic classification would group SCAs 1-3, 6, 7, 12, 17, and DRPLA as polyglutamine (triplet repeat or CAG repeat) disorders; SCAs 8, 10, 31, and 36 as other repeat types; SCAs 4, 5, 11-16, 23, 27, and GSS as resulting from other mutation types; and SCAs 6, 13, 19, 22, and EA-1, 2, and 5 as primary channelopathies. The molecular bases of the remaining SCAs are still unknown (*see Table 4*).

The average age of onset is in the third decade, and, in the early stages, most of these dominantly inherited disorders may be indistinguishable from one another, except by genetic testing (see Tables 5 and 6). There have been efforts to develop algorithms to prioritize genetic testing, with the most statistically sound using Baysian analysis to help predict which of the most common SCAs (SCAs 1, 2, 3, 6, 7, 8) could be expected in a particular clinical situation[8].

Table 4. THE DOMINANTLY INHERITED ATAXIAS – MOLECULAR GENETICS
See **http://neuromuscular.wustl.edu/ataxia/domatax.html** *or* **http://www.ncbi.nlm.nih.gov/pubmed/?term=autosomal+dominant+cerebellar+ataxias** *for most current references*

Ataxic Disorder	Gene Locus	Gene/Product	Mutation	Prevalence
TYPICAL DOMINANT				
SCA1	6p23	Ataxin-1	CAG expansion/coding exon. Normal <39 repeats. Disease-causing >44. If no CAT interruption, disease-causing 39-44	6-27% of dominant ataxias worldwide
SCA2	12q24	Ataxin-2	CAG expansion/coding exon. Normal <33 repeats, with CAA interruption. Disease-causing >33, with no CAA interruption (two patients with interrupted 34 expansion)	13-18% of dominant ataxias worldwide
SCA3/Machado-Joseph disease	14q24.3-q31	Ataxin-3	CAG expansion/coding exon. Normal <41 repeats. Disease-causing >45. Homozygous mutant genes cause earlier onset, more severe disease	23-36% of dominant ataxias worldwide
SCA4	16q22.1	Puratrophin-1. Functions in intracellular signaling, actin dynamics. Targeted to the Golgi apparatus. Mutant protein associated with aggregates in Purkinje cells	Single-nucleotide C-T substitution in 5′ untranslated region	Families in Utah and Germany; six families in Japan with later onset pure cerebellar syndrome
SCA5	11p11-q11	ß-III Spectrin stabilizes the glutamate transporter EAAT4 at the surface of the plasma membrane	Inframe deletions; missense (Leu253Pro)	Lincoln family in US; families in Germany and France
SCA6	19p13	CACNa1A/P/Q type calcium channel subunit (disease mechanisms may result from both CAG repeat and channelopathy processes)	CAG expansion/coding exon. Normal <19 repeats. Disease-causing >19. Homozygous mutant genes cause earlier onset, more severe disease. Allelic with EA-2 *(gene truncations)* and hemiplegic migraine *(missense mutations)*	10-30% of dominant ataxias worldwide
SCA7	3p21.1-p12	Ataxin-7. Component of TFTC-like transcriptional complexes (disease mechanisms may result from both CAG repeat and transcriptional dysregulatory processes)	CAG expansion/coding exon. Normal <28 repeats. Disease-causing >37. Intermediate 28-36, may expand into disease range, especially with paternal transmission	2-5% of dominant ataxias worldwide; may be more common in Sweden and Finland
SCA8	13q21	Normal product is an untranslated RNA that functions as a gene regulator. Evidence for a translated polyglutamine protein (Ataxin-8) from an anti-parallel transcript has also been found	CTG expansion at 3′ end. Normal <80 repeats. Disease-causing 80-300, although expansions in this range occur in non-ataxic persons and in other neurologic diseases. Expansions >300 may not cause disease in SCA8 pedigrees	2-4% of dominant ataxias worldwide; genetic testing results may be open to interpretation
SCA9	Unknown	Unknown	Unknown	One American-English family; ophthalmoplegia, optic atrophy, upper motor neuron, Parkinsonism, posterior column features
SCA10	22q13	Ataxin-10. Gene product essential for cerebellar neuronal survival	Pentanucleotide repeat (ATTCT) expansion in intron 9, probable loss of function mutation. Normal <22 repeats. Disease 800-4500. Intergenerationally more likely to contract than expand	Mexican families (ataxia and epilepsy); five Brazilian families (no epilepsy)
SCA11	15q15.2	Tau tubulin kinase 2 (TTBK2)	Stop, frameshift, insertion, or deletion	Two British families
SCA12	5q31-q33	PPP2R2B/brain specific regulatory subunit of protein phosphatase 2A (serine/threonine phosphatase)	CAG expansion in 5′ untranslated region of gene, possibly upstream from transcription start site and affecting gene transcription. Minimal intergenerational instability	German-American family; may account for up to 7% of ADCA in India
SCA13	19q13.3-q13.4	KCNC3 voltage-gated potassium channel associated with high-frequency firing in fast-spiking cerebellar neurons	Two missense mutations found (R420H and F448L)	French family–seven of eight affected members were women, early-onset with cognitive decline. Filipino family with adult-onset ataxia
SCA14	19q13.4-qter	PRKCG/protein kinase Cγ (serine/threonine kinase)	Missense mutations in conserved residues of C1/exon 4–regulatory domain and in catalytic domain of the enzyme. Increased intrinsic activity of mutant enzyme moves intraneuronal distribution from cytosol to plasma membrane. May reduce expression of ataxin-1 in Purkinje cells, and mutant ataxin-1 may reduce expression of PRKCG	Japanese (axial myoclonus), English/Dutch, Dutch, and French (broader age of onset, cognitive impairment) families described. Incomplete penetrance
SCA15	3p26.1	Inositol 1,4,5-triphosphate receptor, type 1 (ITPR1) Same locus as SCA16, SCA29	Large deletions, missense.	Australian, French & Japanese families; 1% of SCA
SCA16	See SCA15			
SCA17/Huntington disease-like 4	6q27	TATA box-binding protein (DNA binding subunit of RNA polymerase II transcription factor D [TFIID]), essential for the expression of all protein-encoding genes; disease mechanisms may result from both CAG repeat and transcriptional dysregulatory processes)	CAG/CAA expansion. Normal <42 repeats. Disease-causing >45. Intermediate 43-48, with incomplete penetrance. Minimal intergenerational instability. Homozygous mutant genes cause earlier-onset, more severe disease. Variable phenotypes include similarities to Huntington's disease, Parkinson's disease, Alzheimer's disease, and variant Jakob-Creutzfeldt disease	Japanese, German, Italian, and French families
SCA18	7q22-q32	Unknown	Linkage studies with DNA polymorphisms point to location	One Irish-American family
SCA19	1p13.2	KCND3 Allelic with SCA22	Missense	Several Dutch families
SCA20	11q12	Contiguous gene duplication syndrome: Region contains ≥ 12 genes	260-kb duplication at 11q12	Anglo-Celtic family in Australia
SCA21	1p36.33	Transmembrane protein 240 (TMEM240)	Missense and stop	2% of French SCA

Continued Table 4. THE DOMINANTLY INHERITED ATAXIAS – MOLECULAR GENETICS
See **http://neuromuscular.wustl.edu/ataxia/domatax.html** *or* **http://www.ncbi.nlm.nih.gov/pubmed/?term=autosomal+dominant+cerebellar+ataxias** *for most current references*

ATAXIC DISORDER	GENE LOCUS	GENE/PRODUCT	MUTATION	PREVALENCE
SCA22	See SCA19			
SCA23	20p13	Prodynorphin (PDYN)	Missense	Dutch families
SCA24 (reserved)				
SCA25	2p21-p13	Unknown	Linkage studies with DNA polymorphisms point to location	One southern French family. Incomplete penetrance
SCA26	19p13.3	Eukaryotic translation elongation factor 2 (EEF2)	Missense	One family of Norwegian descent
SCA27	13q34	Fibroblast growth factor 14	Missense and frameshift	Dutch, German, and French families
SCA28	18p11.21	AFG3L2 Allelic with: Spastic Ataxia, Myoclonic epilepsy with Neuropathy, Recessive (SPAX5)	Missense, frameshift, small deletions	Multiple families, 3% of SCA
SCA29	See SCA15			
SCA30	4q34.3-q35.1	Candidate gene ODZ3	Unknown	Anglo-Celtic family in Australia
SCA31	16q21	Brain-Expressed, Associated with NEDD4 (BEAN)	Penta-nucleotide (TGGAA)n repeat insertion	Third most common SCA in Japan (previously called SCA4)
SCA32	7q32-q33	Unknown	Unknown	One Chinese family
SCA33 (reserved)				
SCA34	6q14.1	Elongation of very long chain fatty acids-like 4 (ELOVL4) Allelic with recessive Ichthyosis, Intellectual Disability & Spastic Quadriplegia	L168F; incomplete penetrance	French-Canadian family
SCA35	20p13	Protein-glutamine gamma-glutamyltransferase 6 (TGM6)	Missense	Two Chinese families
SCA36	20p13	Nuclear Protein 56 (NOP56; NOL5A)	Expansions of Intronic GGCCTG repeat: 25 to 2500	>20 families; Japan, Spain, France
SCA37	1p32	Unknown	Unknown	One Spanish family
SCA38	6p12.1	Elongation of very long chain fatty acids-like 5 (ELOVL5)	Leu72Val; Gly230Val	Four Italian and French families
SCA39	Reserved			
SCA40	14q32.11	Coiled-coil domain-containing protein 88C (CCDC88C; Daple) Allelic with: Hydrocephalus, nonsyndromic, Recessive 1 (HYC1)	Missense, R464H	One Hong Kong China family
EPISODIC				
EA-1	12p13	KCNA 1/potassium voltage-gated channel component. Interictal myokymia	Missense mutations cause altered neuronal excitability in CNS and PNS	Rare families worldwide
EA-2	19p13.2	CACNa1A/P/Q type voltage-gated calcium channel subunit. Interictal nystagmus. Acetazolamide-responsive	Point mutations in exons and introns (nonsense, missense) and small deletions; mutations cause reduced calcium channel activity in CNS and PNS. Allelic with familial hemiplegic migraine and SCA6; two families with CAG expansion and phenotype of episodic ataxia	Rare families worldwide. De novo mutations in 25% of cases
EA-3	1q42	Unknown. Kinesogenic. Vertigo, tinnitus. Interictal myokymia. Acetazolamide-responsive	Unknown	Canadian Mennonite family
EA-4 (PATX)	Not identified	Unknown	Linkage excluded to EA-1 and EA-2. Clinically different from EA-3	North Carolina Families
EA-5	2q23.3	CACNB4ß4/P/Q type voltage-gated calcium channel subunit; two domains interact with a1 subunit	Point mutations leading to amino acid substitution or premature stop codon; mutations cause altered calcium channel activity in CNS	French-Canadian family (phenotype similar to EA-2 with later-onset, incomplete penetrance). German family with seizures. Michigan family with phenotype of juvenile myoclonic epilepsy (premature stop codon)
EA-6	5p13.2	SLC1A3 (EAAT1 protein). Glial glutamate transporter (GLAST). Mutation: reduced capacity for glutamate uptake	Missense mutation; 1047C to G; Pro>Arg	Episodic ataxia, hemiplegia, migraine, seizures
EA-7	19q13	Unknown	Unknown	One American family
EA-8		Unknown	Unknown	Irish family
ATYPICAL DOMINANT				
DRPLA	12p13.31	Atrophin-1. Required in diverse developmental processes; interacts with even-skipped homeobox 2 repressor function	CAG expansion/coding exon. Normal <26. Disease-causing >49. Intermediate 37-48, may expand into disease range, especially with paternal transmission. Homozygous mutant genes cause earlier-onset, more severe disease; homozygous intermediate genes may cause a recessive predominantly spinal syndrome. Allelic with Haw River syndrome (no seizures)	1-5% of dominant ataxias worldwide; 10-20% of ADCA in some areas of Japan
GSS	20p12	PrP/Prion Protein	Point mutations causing amino acid substitutions in PrP or octapeptide insertions, resulting in proteinase K resistant for of protein which accumulates in CNS	Rare families worldwide

Table 5. THE DOMINANTLY INHERITED ATAXIAS ASSOCIATED FEATURES IN DIFFERENTIAL DIAGNOSIS	
Ataxic Disorder	**Typical Associated Clinical Features Beyond Ataxia and Dysarthria**
SCA1	Hyperreflexia/spasticity, cerebellar tremor, dysphagia, optic atrophy
SCA2	Slow saccades, hyporeflexia, cerebellar tremor, parkinsonism, dementia
SCA3	Nystagmus, spasticity (onset <35y), neuropathy (onset >45y), basal ganglia features, lid retraction, facial fasciculations
SCA4	Sensory axonal neuropathy, pyramidal signs
SCA5	Bulbar signs, otherwise predominantly cerebellar
SCA5	Nystagmus (often downbeat), otherwise predominantly cerebellar, onset >50y
SCA7	Macular pigmentary retinopathy, slow saccades, pyramidal signs
SCA8	Nystagmus, cerebellar tremor
SCA9	(reserved)
SCA10	Nystagmus, seizures
SCA11	Nystagmus, hyperreflexia
SCA12	Nystagmus, arm tremor, hyperreflexia
SCA13	Nystagmus, hyperreflexia, mental and motor retardation, childhood onset (adult onset is without retardation)
SCA14	Head tremor or myoclonus
SCA15	Nystagmus, hyperreflexia
SCA16	Nystagmus, head and hand tremor
SCA17	Dementia, psychosis, extrapyramidal features, hyperreflexia, seizures
SCA18	Nystagmus, Babinski sign, sensorimotor axonal neuropathy
SCA19	Cognitive impairment, nystagmus, tremor, myoclonus
SCA20	Palatal tremor, dysphonia
SCA21	Cognitive impairment, extrapyramidal features, hyporeflexia
SCA22	Nystagmus, hyporeflexia
SCA23	Slow saccades, pyramidal signs, sensory neuropathy
SCA24	(reserved)
SCA25	Nystagmus, sensory neuropathy, gastric pain and vomiting
SCA26	Predominantly cerebellar
SCA27	Limb tremor, orofacial dyskinesia, cognitive/behavioral/mood changes
SCA28	Pyramidal signs, ophthalmoparesis
SCA29	Tremor, myoclonus
SCA30	Predominantly cerebellar
SCA31	Predominantly cerebellar
SCA32	Cognitive impairment, azospermia
SCA33	(reserved)
SCA34	Skin disorder, polyneuropathy
SCA35	Upper motor neuron, position sense, torticollis
SCA36	Muscle atrophy, fasciculations, hearing loss, cognitive changes
SCA37	Abnormal vertical eye movements
SCA38	Polyneuropathy
SCA39	(reserved)
SCA40	Limited upgaze, upper motor neuron
EA-1	Brief episodes of ataxia or choreoathetosis, interictal neuromyotonia. Phenytoin or carbamazepine responsive
EA-2	Episodes of ataxia lasting hours, interictal nystagmus, fatigue/weakness. Acetazolamide responsive
EA-3	Kinesigenic episodes of ataxia and vertigo, with diplopia and tinnitus. Acetazolamide responsive
EA-4	Episodes of ataxia with diplopia and vertigo, defective smooth pursuit. Not acetazolamide responsive
EA-5	Similar to EA-2, but later onset; generalized, absence, and myoclonic seizures. Acetazolamide responsive
EA-6	Episodic ataxia with alternating hemiplegia, migraine, and seizures
EA-7	Episodes of vertigo and weakness lasting hours to days, infrequent attacks
EA-8	Episodes of ataxia and weakness lasting minutes to hours, interictal tremor. Clonazepam responsive
DRPLA	Epilepsy, myoclonus (onset <20y); dementia, psychosis, choreoathetosis (onset >20y)
GSS	Dementia, pyramidal signs

Table 6. THE DOMINANTLY INHERITED ATAXIAS PRIORITIZING GENETIC TESTING AS TESTS CONTINUE TO BECOME AVAILABLE	
Characteristic Feature	**Genetic Syndromes to Consider**
"Pure cerebellar" by phenotype and MRI	SCA 5, 6, 8, 10, 11, 14, 15, 16, 22, 26, 30, 31
Complex phenotype, but pure cerebellar atrophy on MRI	SCA 4,18, 21, 23, 25, 27
Brainstem involvement or atrophy on MRI	SCA 1, 2, 3, 7, 13, DRPLA
Pyramidal involvement, hyperreflexia	SCA 1, 3, 4, 7, 8, 11, 12, 23, 28, 35, 40
Extrapyramidal involvement	SCA 1, 2, 3, 12, 21, 27, 35, DRPLA
Peripheral nerve involvement or hyporeflexia on the basis of spinal long tract changes	SCA 1, 2, 3, 4, 8,12, 18, 19, 21, 22, 25, 27, 34, 36, 38
Supratentorial features or MRI findings	Cerebral atrophy–SCA 2, 12, 17, 19 Subcortical white matter changes–DRPLA Dementia–SCA 2, 7, 13, 17, 19, 21, DRPLA, FXTAS; or milder cognitive defects–SCA 1, 2, 3, 6, 12, 32, 36 Mental retardation–SCA 13, 21, 27 Seizures–SCA 7, 10, 17, EA-5 and 6, DRPLA Psychosis–SCA 3, 17, 27, DRPLA
Ocular features	Slow saccades–SCA 1, 2, 3, 7, 17, 23, 28 Abnormal vertical eye movements—37, 40 Downbeat nystagmus–SCA 6, EA-2 Maculopathy–SCA 7
Prominent postural/action tremor	SCA 2, 8, 12, 16, 19, 21, 27, FXTAS Palatal tremor–SCA20 (dentate calcification) Myoclonus–SCA 1, 2, 3, 6, 7,14,19, 29, DRPLA
Episodic features	EA1-8, SCA 6
Early onset (<20y) (Most SCAs can have rare cases with early onset)	Childhood–SCA 2, 7, 13, 25, 27, DRPLA Young adult–SCA 1, 2, 3, 21
Late onset (>50y) (Most SCAs can have rare cases with late onset)	SCA 6, FXTAS, SCA 36, 37, 38
Rapid progression (death in <10y) (Average progression to disability is 5-10y; to death, 10-20y)	Early onset SCA 2, 3, 7, DRPLA
Slow progression over decades	SCA 4, 5, 8, 11, 13, 14, 15, 16, 18, 20, 21, 22, 23, 26, 27, 28, 30, 31, 36, 37 Normal lifespan–SCA 5, 6, 11, 18, 26, 27, 28
Anticipation/intergenerational DNA instability (usually paternal>maternal; maternal>paternal indicated by (m))	SCA 1, 2, 3, 4, 5 (m), 6 (not due to repeat size), 7, 8 (m), 10,19, 20, 21, 22, DRPLA
Variable phenotype	SCA 2, 3, 4, 5, 7, 14, 15, 17, GSS

SCA3 is the most common dominant ataxia in North America, followed by SCAs 6, 2, and 1. Gene testing is currently commercially available for only 14 of the SCAs, but screening for SCAs 1, 2, 3, and 6 will identify a mutant gene in about 50 percent of familial cases[9].

Online resources to find commercial laboratories performing SCA testing can be found at www.genetests.org. These tests may cost several hundred dollars apiece—and the entire battery of available tests could cost several thousand dollars, posing a financial barrier to exact diagnosis in many cases[10].

The clinical use of next-generation exome sequencing is becoming more widespread. It might prove a less expensive and more comprehensive technology for the identification of non-repeat disorders. However, there is limited information available to direct clinicians in identifying which patients would most benefit from such testing. Findings suggest that patients with chronic progressive cerebellar ataxia would benefit diagnostically from exome sequencing irrespective of a positive family history or early age at onset. Strategies for the integration of genomic testing into the clinical evaluation and effective bioinformatics methods of data analysis are being developed[11, 12, 13].

Recessively inherited ataxias[14,15]

- **Friedreich's ataxia-like syndromes[16]**
- **Early onset cerebellar ataxia (EOCA)[17]**

The recessive ataxias are most often onset before the age of 25. The most common of the recessively inherited ataxias is Friedreich's ataxia (FRDA), with an incidence of 1 in 30,000-50,000. Carrier frequency is 1 in 60-110. It is rare in Asian and African pedigrees.

In some populations, **ataxia with oculomotor apraxia types 1 and 2 (AOA1, AOA2)** also are found with high frequency.

Before the age of 5, **Ataxia-telangiectasia** is the most common recessively inherited cause of cerebellar ataxia[18,19].

In young children, however, the most common cause of ataxia remains acute viral/post-viral cerebellar ataxia, which is self-limited and recovers in most within three to four weeks[20].

The diagnostic criteria for these disorders are listed in Table 7, with the molecular genetic features listed in Table 8.

Table 7. THE RECESSIVELY INHERITED ATAXIAS DIFFERENTIAL DIAGNOSIS

Classic Friedreich's Ataxia (FRDA)	**Friedreich's Ataxia-Like Syndromes** Criteria that differ from FRDA	**Early Onset Cerebellar Ataxia (EOCA)** Criteria that differ from FRDA
Criteria from Anita Harding's work a (percentages vary slightly by study) Recessive or sporadic inheritance		*Criteria from Anita Harding's work d*
Onset by age 25 (85%)	Onset between 2 and 20 years of age	Onset between 2 and 20 years of age
Caudal to rostral progressive ataxia (100%)	Caudal to rostral progressive ataxia	Pancerebellar onset
Eye movements show saccade intrusions	Eye movements may or may not show nystagmus	Eye movements show nystagmus or oculomotor apraxia
Dysarthria (95%)		
Absent deep tendon reflexes (75%) Extensor plantar response (80%)	Absent lower limb reflexes with extensor plantar response	May have retained or brisk lower limb DTRs and extensor plantar response
Weakness later in disease, esp. lower extremities (67-88%)	Weakness may or may not be seen	Weakness usually seen, often presenting early in the disease
Posterior column sensory loss (~80%), with electrical evidence for axonal sensorimotor neuropathy	Decreased vibratory sensation, axonal sensory neuropathy	Sensory changes less commonly seen
Scoliosis (60-80%); pes cavus (50-75%)		
Abnormal EKG (65%) Diabetes mellitus (10%)	May or may not have cardiomyopathy, but does not have diabetes	No cardiomyopathy Only A-T has diabetes
No cerebellar atrophy on MRI (90%)	May or may not have cerebellar atrophy on MRI	Has cerebellar atrophy on MRI
In a recent confirmatory study b • 90% of individuals with >50% of criteria were gene positive for FRDA • 50% of individuals with 50% of criteria were gene positive for FRDA • 10% of individuals with <50% of criteria were gene positive for FRDA There are case reports of genetically confirmed FRDA with very late onset, slower progression (Acadian variant), spasticity, demyelinating neuropathy, or chorea. FRDA is caused by a GAA triplet expansion or point mutation (3%) in the first intron of the FRDA gene on chromosome 9q13, resulting in reduced gene product (frataxin). Frataxin is a mitochondrial protein involved in iron-sulfur cluster assembly. Its deficiency is associated with mitochondrial iron accumulation, increased sensitivity to oxidative stress, deficiency of respiratory chain complex activities, and impairment of tissue energy metabolism c.	Includes several distinctive syndromes: • Vitamin E-associated syndromes (ataxia with vitamin E deficiency [AVED], aß- or hypoß-lipoproteinemias) • Refsum's disease • Late-onset Tay-Sachs (ß-hexo-saminidase A deficiency LOTS) • Cerebrotendinous xanthomatosis (CTX) • DNA polymerase y related disorders (MIRAS) • Infantile onset spinocerebellar ataxia (IOSCA)	Includes several distinctive syndromes: • Ataxia-telangiectasia (AT) and AT-like disorder (ATLD-MRE11) e • Ataxia with oculomotor apraxia types 1 & 2 (AOA1, AOA2) f • Complicated hereditary spastic paraplegias (e.g. ARSACS) • Late-onset inborn errors of (e.g. - adrenomyeloneuropathy (AMN/ALD-X linked) - Hartnup's disease - Hemochromatosis - Lysosomal storage (Niemann-Pick Type C, metachromatic leukodystropy [MLD], Krabbe's) - Oxidative disorders - Sandhoff's disease - Sialidosis - Wilson's disease

a Harding, A.E. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. *Brain*, 1981. **104**(3): p. 589-620.

b Geschwind, D.H., et al. Friedreich's ataxia GAA repeat expansion in patients with recessive or sporadic ataxia. *Neurology,* 1997. **49**(4): p. 1004-09.

c Voncken, M., P. Ioannou, and M.B. Delatycki. Friedreich ataxia-update on pathogenesis and possible therapies. *Neurogenetics*, 2004. **5**(1): p. 1-8.

d Harding, A.E. Early onset cerebellar ataxia with retained tendon reflexes: a clinical and genetic study of a disorder distinct from Friedreich's ataxia. *J Neurol Neurosurg Psychiatry*, 1981. **44**(6): p. 503-08.

e Chun, H.H., and R.A. Gatti. Ataxia-telangiectasia, an evolving phenotype. *DNA Repair (Amst)*, 2004. 3(8-9): p. 1187-96.

f Le Ber, I., A. Brice, and A. Durr. New autosomal recessive cerebellar ataxias with oculomotor apraxia. *Curr Neurol Neurosci Rep*, 2005. **5**(5): p. 411-17.

Table 8. THE RECESSIVELY INHERITED ATAXIAS MOLECULAR GENETICS						
Phenotype	**Ataxic Disorder**	**Disease Abbr.**	**Gene/Protein**	**Gene Abbr**	**Locus**	**Protein Function**
Friedreich Ataxia-like	Friedreich's ataxia	FRDA	Frataxin	FXN	9q13	Mitochondrial iron metabolism
	Ataxia with vitamin E deficiency	AVED	a-Tocopherol transfer protein	TTPA	8q13.1-q13.3	Vitamin E homeostasis
	Abetalipoproteinemia	ABL	Microsomal triglyceride transfer protein	MTP	4q22-q24	Lipoprotein Metabolism
	Refsum's disease	-	Phytanoyl-CoA hydroxylase	PHYH	10oter-p11.2	Fatty acid oxidation
			Peroxisome biogenesis factor 7	PEX7	6q22-q24	Peroxisomal protein importation
Friedreich Ataxia-like with cerebellar atrophy	Late-onset Tay-Sachs disease	LOTX	ß-Hexosaminidase A	HEXA	15Q23-Q24	Glycosphingolipid metabolism
	Cerebrotendinous xanthomatosis	CTX	Sterol-27 hydroxylase	CYP27	2q33-qter	Bile acid syntheses
	DNA polymerase y related disorders	MIRAS	DNA polymerase y-1	POLG1	15q 24-q26	Mitochondrial DNA repair/replication
	Infantile onset spinocerebellar ataxia	IOSCA	Twinkle,Twinky	C10orf2	10q24	DNA replication, unknown
Early onset cerebellar ataxia with retained reflexes (EOCARR)	Ataxia-telangiectasia	AT	Ataxia-telangiectasia, mutated	ATM	11q22-q23	DNA damage response
	Ataxia-telangiectasia-like disorder	ATLD	Meiotic recombination 11	MRE11	11q21	DNA damage response
	Ataxia with oculomotor apraxia type 1	AOA1	Aprataxin	APTX	9p13.3	DNA repair, ?RNA processing
	Ataxia with oculomotor apraxia type 2	AOA2	Senataxin	SETX	9Q34	?DNA repair, ?DNA transcription, ?RNA processing
	Autosomal recessive ataxia of Charlevoix-Saguenay	ARSACS	Sacsin	SACS	13q12	?Protein folding

Maternally inherited ataxias (X-linked and mitochondrial)

These forms of ataxia are suspected when the defective genetic material seems always to come down from the mother's side of the family. She may or may not be symptomatic herself. Her sons and daughters are equally at-risk to inherit the disease gene.

In X-linked disorders the female carriers may not develop symptoms. Affected males with X-linked disorders will never pass the defective gene on to their sons (no male-to-male transmission), but will always pass it on to their daughters, who then become carriers and may or may not develop symptoms. The presence of male-to-male transmission rules out an X-linked ataxia.

In genetic disorders of the mitochondrial genome, phenotype severity depends on the ratio of abnormal to normal mitochondria. As all mitochondria are inherited from the mother, an affected male can never pass on the disease to his children. Most mitochondrial genes, however, are coded in the autosomal genome, causing disorders that can be transmitted like other dominant or recessive diseases[21,22].

The most common maternally inherited ataxias are outlined in *Table 9*.

Table 9. MATERNALLY INHERITED ATAXIAS X-LINKED AND MITOCHONDRIAL						
Ataxic Disorder	**Disease Abbr.**	**Gene/Protein**	**Gene Abbr.**	**Locus**	**Protein Function**	**Phenotype**
Sideroblastic anemia	XLSA/A	ATP-binding cassette 7 transporter	ABCB7	Xq13	Mitochondrial iron transfer from matrix to intermembrane space	Infantile-onset nonprogressive ataxia with upper motor neuron signs and anemia
Pyruvate dehydrogenase complex deficiencies	PDHC	5 gene/protein complex- • E1-pyruvate decarboxylase • E2-dihydrolopoyl transacetylase • E3-lipoamide dehydrogenase • Pyruvate dehydrogenase phosphatase • E3 binding protein	PDHA1 DLAT DLD - PDHX	Xp22.2 - 7q31 - 11p13	Complex links glycolysis with the tricarboxylic acid (TCA) cycle and catalyzes the irreversible conversion of pyruvate to acetyl-CoA	Early onset with episodic ataxia, seizures, and lactic acidosis
Pelizaeus Merzbacher	PMD null syndrome; SPG2	Proteolipid protein	PLP	Xp22	Formation and maintenance of myelin	Onset infancy to adulthood with spastic paraparesis, ataxia, optic atrophy, cognitive decline
Adrenomyelo-neuropathy	AMN	ATP binding transporter in peroxisomal membrane	ALDP	Xq28	Defect allows accumulation of very long chain fatty acids	Adult onset spastic paraparesis, axonal neuropathy, adrenal insufficiency
Fragile X-associated tremor/ataxia syndrome	FXTAS	Fragile X mental retardation gene-premutation CGG expansion (69-135 repeats; full mutation is >200)	FMR1	Xq27.3	Results in elevated FMR1 mRNA levels and slightly lowered level of FMRI protein	Males >50 y/o with tremor (action or resting), ataxia, executive dysfunction. May resemble MSA. MRI with T2 signal intensity in cerebellar white matter
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes	MELAS	tRNA leucine	-	mtDNA	Mitochondrial dysfunction; capillary angiopathy	Mitochondrial encephalomyopathy, lactic acidosis, stroke; migraine-like attacks, seizures
Myoclonic epilepsy associate with ragged red fibers	MERRF	tRNA lysine tRNA serine	-	mtDNA	Mitochondrial dysfunction	Myoclonic epilepsy with ragged red fiber and ataxia
Neuropathy, ataxia and retinitis pigmentosa	NARP	ATPase 6	-	mtDNA	Complex V	Neuropathy, ataxia, retinitis pigmentosa
Coenzyme Q10 deficiency	CoQ10 deficiency	-	-	9p13	Cofactor for Complex II	Early onset ataxia, myopathy, spasticity, seizures, mental retardation. Serum coQ10 levels 1/3 of nl
Variable complex deficiencies Deletions or point mutations affecting mtDNA related components	e.g. Cytochrome C oxidase deficiency; Kearns-Sayre syndrome	Complex I Complex II Complex III Complex IV Complex V	-	mtDNA	Defects cause disruption of mitochondrial electron transport chain, causing oxidative stress	Early to adult onset ataxia, external ophthalmoplegia, retinal degeneration, hearing loss, heart block, myopathy, cognitive decline. Lactic acidosis. Ragged red fibers on muscle biopsy

Sporadic ataxias

In all age ranges and populations, nongenetic ataxia is more common than inherited ataxia, often by a ratio of 2:1. *(See Table 1 for identifiable nongenetic etiologies.)* With thorough evaluation *(see Table 3),* a treatable cause might be found, but the majority of these syndromes remain idiopathic. Their classification is outlined in *Table 10*.

Table 10. CLASSIFICATION OF THE SPORADIC ATAXIAS

Type	Classification
Sporadic ataxia with identifiable genetic cause (2-29% in various studies)	SCA 1-28, with missing family history (SCA6 most commonly found)
	Any recessively inherited ataxia (FRDA, AOA 1 or 2, ataxia-telangiectasia most commonly found)
	Any X-linked or mitochondrially inherited ataxia (FXTAS most commonly found)
Sporadic ataxia with known acquired cause	(see Table1)
Idiopathic cerebellar ataxia, according to Harding[a]	Type A – with dementia; ddx-parenchymatous cerebellar cortical atrophy, prion diseases, Whipple's disease, inborn errors of metabolism
	Type B – with tremor; ddx-FXTAS
	Type C – sporadic olivopontocerebellar atrophy; multiple system atrophy; other Parkinson-plus syndromes (PSP)
Idiopathic late-onset cerebellar atrophy (ILOCA)[b]	

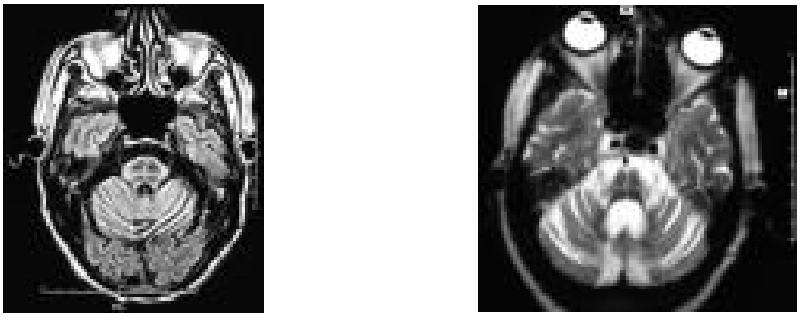
a Harding, A.E. "Idiopathic" late onset cerebellar ataxia. A clinical and genetic study of 36 cases. *J Neurol Sci*, 1981. **51**(2): 259-71.
b Klockgether, T. Sporadic ataxia with adult onset: classification and diagnostic criteria. *Lancet Neurol*. 2010 Jan;**9** (1):94-104.

The most reliable approach to sporadic ataxia is to assign a phenotype by history and physical, imaging, and electrodiagnostics; obtain a detailed family and environmental history; rule out known acquired causes; and consider genetic testing. Then, wait and watch, and treat bothersome symptoms[23-25].

Of patients with idiopathic late-onset cerebellar ataxia (ILOCA), 25 percent will go on to develop multiple system atrophy (MSA), with the emergence of symptoms of L-dopa-unresponsive parkinsonism and autonomic failure[26-29]. Autonomic involvement will be confirmed by orthostatic blood pressure changes, lower motor neuron bowel and bladder dysfunction, and abnormalities in testing for heart rate variability, tilt table, sympathetic skin response/sweating, and cardiac I-123-MIBG-SPECT. REM sleep disturbances or erectile dysfunction may precede ataxia by 5-10 years. Obstructive sleep apnea and stridor are common. Notable cerebellar disability is seen within 2-3 years. Dopa-PET scans will confirm basal ganglia involvement, but MRI scanning may show the earliest signs of impending MSA. Hot cross bun sign in pons and hyper/ hypo-intensities in putamen correlate strongly with MSA *(see Figure 1)*. The presence of dementia, ophthalmoplegia, or chorea suggest something other than MSA.

Patients with MSA also may emerge from the Parkinson's population, with the evolution of ataxia and autonomic signs. Of patients diagnosed with MSA, 80 percent start with signs of Parkinson's; 20 percent of patients diagnosed with MSA start with ataxia. Shy-Drager syndrome *(initial presentation with autonomic failure)* is less commonly seen.

Figure 1. HOT CROSS BUN SIGN IN PONS



T1 T2

MRI T1 and T2 images

Treatment of the ataxic patient

It is important for the patient and family to have some idea what to expect and to know what to watch for. Progression is variable and can be slower in some patients and more rapid in others. In a worst case scenario, untreatable rigidity, autonomic failure, and bulbar symptoms (central or obstructive apneas, stridor, choking/aspiration) can lead to death in under a year. Interventions to manage difficult symptoms should be discussed, for example, continuous positive airway pressure devices, tracheostomy, feeding tube. Increased falling or becoming chair- or bed-bound may lead to life-threatening complications (injuries, decubiti, infection, blood clots). Dementia, behavioral problems, and depression make management, compliance, and care more difficult.

Symptomatic management should always be pursued and is helpful for nystagmus, dizziness, spasticity, rigidity, tremor, pain, fatigue, orthostasis, bowel and bladder dysfunction, and sexual dysfunction. Open-label and controlled trials have been conducted for some agents to improve balance and coordination, and these can be tried in off-label indications (amantadine and buspirone have been studied most extensively; riluzole and varenicline also have published studies).

There are as yet no approved disease-modifying therapies for any of the genetic ataxias, although research has been aggressive and will provide such therapies in the upcoming years. Acquired ataxias can be treated specific to the cause (infectious, inflammatory, immune-mediated, toxic, metabolic), but neuronal loss cannot be restored at this time. Research in growth factors and stem cells will provide possible replacement strategies in the future.

Rehabilitation resources are widely available and very helpful in most ataxic illnesses. These could include physical, occupational, and speech/swallowing therapy; aids to gait and activities of daily living; safety interventions; individual educational programs with schools; nutrition counseling; ophthalmology assessment; home health assistance; genetic and psychosocial counseling; legal aid; support groups; and special assistance and support for the caregiver.

Sincere effort should be applied to answering the patient's and family's questions as honestly and completely as possible *(What do I have? What is the cause? Are my children at risk? Can it be cured? Will it get worse? How bad will it get? How soon? Is there any research being done?)* No one should be told that there is nothing that can be done.

Resources to aid in the evaluation of the ataxic patient

- **NCBI PubMed**
  Website: www.ncbi.nlm.nih.gov/entrez/query
- **Online Mendelian Inheritance in Man/OMIM**
  Website: www.ncbi.nlm.nih.gov/omim
- **GeneReviews**
  Website: www.genetests.org
- **Neuromuscular Disease Center**
  Neuromuscular Division Box 8111—Neurology
  660 South Euclid Avenue, Saint Louis, MO 63110
  Telephone: 314-362-6981
  Website: www.neuro.wustl.edu/neuromuscular
- **National Ataxia Foundation**
  2600 Fernbrook Lane, Suite 119, Minneapolis, MN 55447
  Telephone: 763-553-0020
  Website: www.ataxia.org
- **Friedreich's Ataxia Research Alliance**
  P.O. Box 1537, Springfield, VA 22151
  Telephone: 703-426-1576
  Website: www.curefa.org

References for treatment of the ataxic patient

The following reference materials provide helpful information. Despite vigorous research, there are still no disease-modifying therapies or approved symptomatic treatments for cerebellar ataxia

- G.Grimaldi,G.P Argyropoulos, A. Boehringer et al. Non-invasive cerebellar stimulation--a consensus paper. *Cerebellum.* 2014 Feb;13 (1):121-38.
- S. Manek, MD, and M.F. Lew, MD. "Gait and Balance Dysfunction in Adults." In *Movement Disorders,* 2003, 5:177-185.
- M. Nance, MD. *Living With Ataxia: An Information and Resource Guide.* 2nd edition. National Ataxia Foundation, 2003.
- M. Ogawa. "Pharmacological Treatments of Cerebellar Ataxia." In *Cerebellum,* 2004, 3:107-11.
- S.L. Perlman, MD. "Cerebellar Ataxia." In *Current Treatment Options in Neurology,* 2000, 2:215-224.
- S.L. Perlman, MD. "Symptomatic and Disease-Modifying Therapy for the Progressive Ataxias." In *The Neurologist,* 2004, 10:275-89.
- G.N. Rangamani, PhD, CCC-SLP. "*Managing Speech and Swallowing Problems: A Guidebook for People With Ataxia.*" 2nd edition. National Ataxia Foundation, 2006.
- M. Synofzik and W. Ilg. "Motor training in degenerative spinocerebellar disease: ataxia-specific improvements by intensive physiotherapy and exergames." In *Biomed Res Int.* 2014; 2014:583507.
- M.M.Trujillo-Martín, P. Serrano-Aguila, F.Monton-Alvarez et al. "Effectiveness and safety of treatments for degenerative ataxias: a systematic review." In *Mov Disord*. 2009 Jun 15;24(8):1111-24.
- B.P. Van de Warrenburg, J. van Gaalen, S. Boesch, et al. "EFNS/ENS Consensus on the diagnosis and management of chronic ataxias in adulthood." In *Eur J Neurol.* 2014 Apr;21(4):552-62.

References

1. Moseley, M.L., et al. Incidence of dominant spinocerebellar and Friedreich triplet repeats among 361 ataxia families. *Neurology,* 1998. 51(6): p. 1666-71.
2. Schols, L., et al. Genetic background of apparently idiopathic sporadic cerebellar ataxia. *Hum Genet,* 2000. 107(2): p. 132-37.
3. Abele, M., et al. The aetiology of sporadic adult-onset ataxia. *Brain,* 2002. 125(Pt 5): p. 961-68.
4. Hall, D.A., et al. Initial diagnoses given to persons with the fragile X-associated tremor/ataxia syndrome (FXTAS). *Neurology,* 2005. 65(2): p. 299-301.
5. Van Esch, H., et al. Screening for FMR-1 premutations in 122 older Flemish males presenting with ataxia. *Eur J Hum Genet,* 2005. 13(1): p. 121-23.
6. Hagerman, P.J., and R.J. Hagerman. Fragile X-associated tremor/ataxia syndrome (FXTAS). *Ment Retard Dev Disabil Res Rev,* 2004. 10(1): p. 25-30.
7. Hagerman, R.J., et al. Fragile X-associated tremor/ataxia syndrome (FXTAS) in females with the FMR1 premutation. *Am J Hum Genet,* 2004. 74(5): p. 1051-56.

8. Maschke, M., et al. Clinical feature profile of spinocerebellar ataxia type 1-8 predicts genetically defined subtypes. *Mov Disord,* 2005. 20(11): p. 1405-12.
9. Shakkottai VG, Fogel BL. Clinical neurogenetics: autosomal dominant spinocerebellar ataxia. *Neurol Clin*. 2013 Nov;31(4):987-1007
10. Fogel BL, et al. Utilization of genetic testing prior to subspecialist referral for cerebellar ataxia. *Genet Test Mol Biomarkers.* 2013 Aug;17(8):588-94.
11. Lee H, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. 2014 Nov 12;312(18):1880-7.
12. Fogel, BL, et al. Exome sequencing in the clinical diagnosis of sporadic or familial cerebellar ataxia. *JAMA Neurol*. 2014 Oct;71(10):1237-46.
13. Fogel, BL. Interpretation of genetic testing: variants of unknown significance.*Continuum (Minneap Minn).* 2011 Apr;17(2 Neurogenetics):347-52.
14. Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. *Lancet Neurol*. 2007 Mar;6(3):245-57.
15. Fogel, BL. Childhood cerebellar ataxia. *J Child Neurol*. 2012 Sep;27(9):1138-45.
16. Collins, A. Clinical neurogenetics: friedreich ataxia. *Neurol Clin.* 2013 Nov;31(4):1095-120.
17. Poretti, A., et al. Differential diagnosis of cerebellar atrophy in childhood. *Eur J Paediatr Neurol.* 2008 May;12(3):155-67. Epub 2007 Sep 14.
18. Ambrose M, Gatti RA. Pathogenesis of ataxia-telangiectasia: the next generation of ATM functions. *Blood.* 2013 May 16;121(20):4036-45.
19. Chaudhary MW, Al-Baradie RS. Ataxia-telangiectasia: future prospects. *Appl Clin Genet.* 2014 Sep 10;7:159-67.
20. Poretti, A. et al. Acute ataxia in children: approach to clinical presentation and role of additional investigations. *Neuropediatrics*. 2013 Jun;44(3):127-41.
21. Toscano A, Musumeci O. Mitochondrial Disorders in Adults. *Curr Mol Med.* 2014 Oct 10. [Epub ahead of print]
22. Ardissone A,, et al. Mitochondrial Diseases in Childhood. *Curr Mol Med.* 2014 Oct 10. [Epub ahead of print]
23. Fogel BL, Perlman S. An approach to the patient with late-onset cerebellar ataxia. *Nat Clin Pract Neurol.* 2006 Nov;2(11):629-35
24. Fogel, BL, et al. Mutations in rare ataxia genes are uncommon causes of sporadic cerebellar ataxia. *Mov Disord*. 2012 Mar;27(3):442-6.
25. Sedel, F. et al. Therapy insight: inborn errors of metabolism in adult neurology--a clinical approach focused on treatable diseases. *Nat Clin Pract Neurol.* 2007 May;3(5):279-90.
26. Gilman, S., et al. Evolution of sporadic olivopontocerebellar atrophy into multiple system atrophy. *Neurology,* 2000. 55(4): p. 527-32.
27. Gilman, S. et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*. 2008 Aug 26;71(9):670-6.
28. Lin, DJ., et al. Multiple system atrophy of the cerebellar type: clinical state of the art. *Mov Disord.* 2014 Mar;29(3):294-304.
29. Fogel, BL, et al. The neurogenetics of atypical parkinsonian disorders. *Semin Neurol.* 2014 Apr;34(2):217-24.

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ISBN: 978-0-943218-14-4
9 780943 218144 50500

$5.00