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

National Ataxia Foundation
2600 Fernbrook Lane, Suite 119
Minneapolis, MN 55447-4752

Telephone 763-553-0020
Fax 763-553-0167
Email naf@ataxia.org
Website www.ataxia.org

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Contents

About the Author

Dr. Susan L. Perlman is Clinical Professor of Neurology at the David Geffen School of Medicine at UCLA. She received her MD degree from the State University of New York at Stony Brook in 1975 and completed her neurology residency and research fellowship at UCLA in 1981. Her research was in the biochemistry of Friedreich's ataxia. Dr. Perlman has been the director of the UCLA Ataxia Clinic since 1986, where she has engaged in clinical research and has published numerous articles on the inherited and sporadic ataxias. Since 1993 she has been a member of the Medical and Research Advisory Board of the National Ataxia Foundation and is a founding member of the Cooperative Ataxia Group (http://cooperative-ataxia-group.org).

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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 10 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. The treatment of cerebellar ataxia remains primarily a neurorehabilitation challenge (physical, occupational, and speech/swallowing therapy; adaptive equipment; driver safety training; nutritional 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**

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
Infectious/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	Behcet's, giant cell arteritis, lupus, and others
	Paraneoplastic [a]	Anti-Yo, Hu, Ri, MaTa, CV2, Zic 4; anti-calcium channel; anti-CRMP-5, ANNA-1,2,3, mGluR1, TR
	Other autoantibodies	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]
	Anti-immune therapies used in reported cases of immune-mediated cerebellar ataxia	Steroids, plasmapheresis, IVIG, rituximab, mycophenolate mofetil, 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.

(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/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), or because of specific genetic processes that modify disease presentation in the pedigree (anticipation, incomplete penetrance, mosaicism). Genetic studies of

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

Type	Features
Neurologic 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-onset inborn errors of metabolism
	Endocrine – diabetes (FRDA/mitochondrial, Wilson's disease), adrenal insufficiency (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

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].

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, Hgb A1c, 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), alphafetoprotein, 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's 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]

[a] Gray, R.G., et al. Inborn errors of metabolism as a cause of neurological disease in adults: an approach to investigation. *J Neurol 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 29; the episodic ataxias (EA 1-6); 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, 17, and DRPLA as polyglutamine (triplet repeat or CAG repeat) disorders; SCAs 4, 5, 14, 27, and GSS as resulting from point mutations; SCAs 6, 13, and EA-1, 2, and 5 as channelopathies; and SCAs 8, 10, and 12 as repeat expansions outside the coding region that result in decreased gene expression. The molecular bases of SCAs 11, 15, 16, 18-26, and 28-29 are still unknown *(see Table 4 on pages 6-9)*.

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 each other, except by genetic testing *(see Tables 5 and 6 on pages 10 and 11)*. 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].

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 12 of the SCAs, but screening for SCAs 1, 2, 3, and 6 will identify a mutant gene in about 50 percent of familial cases. Online resources to find commercial laboratories performing SCA testing can be found at www.geneclinics.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.

Table 4. THE DOMINANTLY INHERITED ATAXIAS — Molecular Genetics		
Ataxic Disorder	**Gene Locus**	**Gene/ Product**
SCA1[a]	6p23	Ataxin-1
SCA2[b-d]	12q24	Ataxin-2
SCA3/Machado-Joseph disease[e]	14q24.3-q31	Ataxin-3
SCA4[f]	16q22.1	Puratrophin-1. Functions in intracellular signaling, actin dynamics. Targeted to the Golgi apparatus. Mutant protein associated with aggregates in Purkinje cells
SCA5[g]	11p11-q11	ß-III Spectrin stabilizes the glutamate transporter EAAT4 at the surface of the plasma membrane
SCA6[h]	19p13	CACNα1A/P/Q type calcium channel subunit (disease mechanisms may result from both CAG repeat and channelopathy processes)
SCA7[i]	3p21.1-p12	Ataxin-7. Component of TFTC-like transcriptional complexes (disease mechanisms may result from both CAG repeat and transcriptional dysregulatory processes)
SCA8[j]	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
SCA9 (reserved)		
SCA10[k]	22q13	Ataxin-10. Gene product essential for cerebellar neuronal survival
SCA11[l]	15q14-q21.3	Unknown
SCA12[m]	5q31-q33	PPP2R2B/brain specific regulatory subunit of protein phosphatase 2A (serine/threonine phosphatase)
Minimal intergenerational instability		
SCA13[n,o]	19q13.3-q13.4	KCNC3 voltage-gated potassium channel associated with high-frequency firing in fast-spiking cerebellar neurons
SCA14[p]	19q13.4-qter	PRKCG/protein kinase Cγ (serine/threonine kinase)
SCA15[q]	3p26.1-25.3	Unknown. Region may contain gene(s) for three linked or allelic disorders
SCA16[r]	8q22.1-q24.1	Unknown
SCA17/Huntington disease-like 4[s]	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)
SCA18[t]	7q22-q32	Unknown
SCA19[u,v]	1p21-q21	Unknown

	Mutation	Prevalence
	CAG expansion/coding exon. Normal <39 repeats. Disease-causing >44. If no CAT interruption, disease-causing 39-44	6-27% of dominant ataxias worldwide
	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
	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
	Single-nucleotide C-T substitution in 5′ untranslated region	Families in Utah and Germany; six families in Japan with later onset pure cerebellar syndrome
	Inframe deletions; missense (Leu253Pro)	Lincoln family in US; families in Germany and France
	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
	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
	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
	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)
	Linkage studies with DNA polymorphisms point to location; possible evidence of anticipation in one family suggest intergenerational instability	Two British families
	CAG expansion in 5′ untranslated region of gene, possibly upstream from transcription start site and affecting gene transcription. to 7% of ADCA in India	German-American family; may account for up to 7% of ADCA in India
	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
	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
	Linkage studies with DNA polymorphisms point to location	One Australian family (pure cerebellar), two Japanese families (with tremor/myoclonus), and one family with autosomal dominant congenital nonprogressive cerebellar ataxia
	Linkage studies with DNA polymorphisms point to location	One Japanese family
	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
	Linkage studies with DNA polymorphisms point to location	One Irish-American family
	Linkage studies with DNA polymorphisms point to location; possibly allelic with SCA22	One Dutch family

Table 4 continued **THE DOMINANTLY INHERITED ATAXIAS — Molecular Genetics**

Ataxic Disorder	Gene Locus	Gene/ Product
SCA20[w]	11p13-q11	Near SCA5 locus, gene/product unknown
SCA21[x]	7p21-15	Unknown
SCA22[u,y]	1p21-q23	Unknown
SCA23[z]	20p13-12.3	Unknown
SCA24 (reserved)		
SCA25[aa]	2p15-21	Unknown
SCA26[bb]	19p13.3	Unknown
SCA27[cc]	13q34	Fibroblast growth factor 14
SCA28[dd]	18p11.22-q11.2	Unknown
SCA29	3p26	Unknown, may be allelic to SCA15
EA-1[ee]	12p13	KCNA 1/potassium voltage-gated channel component. Interictal myokymia
EA-2[ff]	19p13	CACNa1A/P/Q type voltage-gated calcium channel subunit. Interictal nystagmus. Acetazolamide-responsive
EA-3[gg]	1q42	Unknown. Kinesogenic. Vertigo, tinnitus. Interictal myokymia. Acetazolamide-responsive
EA-4 (PATX)[hh]	Not identified	Unknown
EA-5[ii]	2q22-q23	CACNB4ß4/P/Q type voltage-gated calcium channel subunit; two domains interact with a1 subunit
EA-6[ij]	5p13	SLC1A3 (EAAT1 protein). Glial glutamate transporter (GLAST). Mutation: reduced capacity for glutamate uptake
DRPLA[kk,ll]	12p13.31	Atrophin-1. Required in diverse developmental processes; interacts with even-skipped homeobox 2 repressor function
GSS[mm]	20p12	PrP/prion protein

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	Mutation	Prevalence
	Linkage studies with DNA polymorphisms point to location; repeat expansion detection did not show CAG/CTG or ATTCT/AGAAT repeat expansions.	Anglo-Celtic family in Australia
	Linkage studies with DNA polymorphisms point to location; evidence of anticipation suggests intergenerational instability	One French family
	Linkage studies with DNA polymorphisms point to location; possibly allelic with SCA19, but without cognitive impairment	One Chinese family
	Linkage studies with DNA polymorphisms point to location	One Dutch family
	Linkage studies with DNA polymorphisms point to location	One southern French family. Incomplete penetrance
	No anticipation	One family of Norwegian descent
	Missense and frameshift mutations	Dutch, German, and French families
	No anticipation, one case of incomplete penetrance	One Italian family
	Linkage studies with DNA polymorphisms point to location	Two Japanese families
	Missense mutations cause altered neuronal excitability in CNS and PNS	Rare families worldwide
	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
	Unknown	Canadian Mennonite family
	Linkage excluded to EA-1 and EA-2. Clinically different from EA-3	North Carolina families
	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)
	Missense mutation; 1047C to G; Pro>Arg	Episodic ataxia, hemiplegia, migraine, seizures
	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
	Point mutations causing amino acid substitutions in PrP or octapeptide insertions, resulting in proteinase K resistant form of protein which accumulates in CNS	Rare families worldwide

[v] Verbeek, D.S., et al. Identification of a novel SCA locus (SCA19) in a Dutch autosomal dominant cerebellar ataxia family on chromosome region 1p21-q21. *Hum Genet,* 2002. **111**(4-5): p. 388-93.
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[aa] Stevanin, G., et al. Spinocerebellar ataxia with sensory neuropathy (SCA25) maps to chromosome 2p. *Ann Neurol,* 2004. **55**(1): p. 97-104.
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[gg] Steckley, J.L., et al. An autosomal dominant disorder with episodic ataxia, vertigo, and tinnitus. *Neurology,* 2001. **57**(8): p. 1499-1502.
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[mm] Sy, M. S., P. Gambetti, and B.S. Wong, Human prion diseases. *Med Clin North Am,* 2002. **86**(3): p. 551-71, vi-vii.

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
SCA6	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
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
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
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
Extrapyramidal involvement	SCA 1, 2, 3, 12, 21, 27, 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
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 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 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	EA1-6, 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
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 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

Recessively inherited ataxias

- **Friedreich's ataxia-like syndromes**
- **Early onset cerebellar ataxia (EOCA)**

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.

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.

The diagnostic criteria for these disorders are listed in *Table 7*, with the molecular genetic features listed in *Table 8 on page 14*.

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, but 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.

The most common maternally inherited ataxias are outlined in *Table 9 on pages 15-16*.

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 on page 16*.

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 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-hexosaminidase A deficiency–LOTS) • Cerebrotendinous xanthomatosis (CTX) • DNA polymerase γ 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 metabolism (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's 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	10pter-p11.2	Fatty acid oxidation
			Peroxisome biogenesis factor 7	PEX7	6q22-q24	Peroxisomal protein importation
Friedreich's ataxia-like with cerebellar atrophy	Late-onset Tay-Sachs disease	LOTS	ß-Hexosaminidase A	HEXA	15q23-q24	Glycosphingolipid metabolism
	Cerebrotendinous xanthomatosis	CTX	Sterol-27 hydroxylase	CYP27	2q33-qter	Bile acid synthesis
	DNA polymerase *y* related disorders	MIRAS	DNA polymerase *y*-1	POLG1	15q24-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

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-dihydrolipoyl 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 levels of FMR1 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

Table 9 *(continued)* MATERNALLY INHERITED ATAXIAS Mitochondrial Point Mutations						
Ataxic Disorder	**Disease Abbr.**	**Gene/Protein**	**Gene Abbr.**	**Locus**	**Protein Function**	**Phenotype**
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 associated 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

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 Table 1)
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)

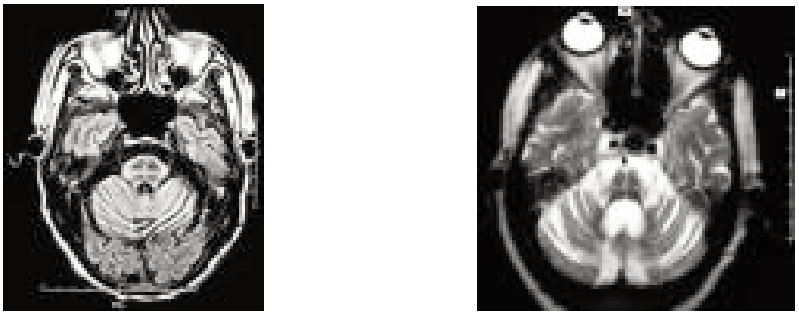
[a] Harding, A.E. "Idiopathic" late onset cerebellar ataxia. A clinical and genetic study of 36 cases. *J Neurol Sci,* 1981. **51**(2): p. 259-71.

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.

Of patients with late-onset cerebellar ataxia, 25 percent will go on to develop multiple system atrophy (MSA), with the emergence of symptoms of L-dopa-unresponsive parkinsonism and autonomic failure[9, 10]. 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).

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.geneclinics.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

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National Ataxia Foundation

600 Highway 169, Suite 1725
Minneapolis, MN 554426
Telephone: 763-553-0020
Fax: 763-553-0167
E-mail: naf@ataxia.org
www.ataxia.org

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