***Ataxias***

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**Ataxias** - wide spectrum of disorders:

* **slowly progressive ataxia that usually begins in legs** is leading symptom.
* pathological hallmark - degeneration / malformation of ***cerebellum*** and/or its ***related structures*** (e.g. brain stem, spinal pathways).
* additional lesions elsewhere frequently are present (esp. *peripheral neuropathies*).
* *no specific treatment*!
  + trials with 5-hydroxytryptophan, amantadine, buspirone may be attempted, although no controlled trials clearly demonstrate efficacy.
  + physical therapy!

Classification of Ataxias

clinical classification introduced by Harding (1983):

# HEREDITARY ATAXIAS

## I. Autosomal recessive ataxias – early-onset ataxias.

1. **Friedreich's ataxia** - 9q13-21 (intronic GAA repeat expansion – gene X25 coding mitochondrial protein **frataxin**)
2. **Early-onset cerebellar ataxias with retained tendon reflexes**
3. **Congenital ataxias** (due to *cerebellar malformations*)
4. **Ataxia-telangiectasia** - 11q22-23 (gene ATM)
5. **Ataxias due to vitamin E deficiency** - 8q (gene for **α-tocopherol transport protein**)

**II. Autosomal dominant cerebellar ataxias (ADCA)** – late-onset ataxias.

1. **Without retinal degeneration**
   1. **with additional noncerebellar symptoms (ADCA-I)**

**SCA1** - 6p21.3 (CAG repeat expansion - gene coding **ataxin-1**)

**SCA2** - 12q23-24.1 (CAG repeat expansion - gene coding **ataxin-2**)

**SCA3 (Machado-Joseph disease)** - 14q32.1 (CAG repeat expansion - gene coding **ataxin-3**)

**SCA4** - 16q24

* 1. **with pure cerebellar syndrome (ADCA-III)**

**SCA5** - 11cen (mutation and gene unknown)

**SCA6** - l9p13.1 (CAG repeat expansion – gene for **α1A voltage-dependent Ca2+ channel**)

1. **With retinal degeneration (ADCA-II)**

**SCA7** - 3p14-21.1 (CAG repeat expansion – gene for **ataxin-7**)

1. **Dentatorubral-pallidoluysian atrophy** - 12p12.3-13.1 (CAG repeat expansion; gene for **atrophin**)
2. **Episodic ataxias (EA)**

**EA-1** - 12p (mutation – gene for **K+ channel**)

**EA-2** - l9p13.1 (mutation – gene for **α1A voltage-dependent Ca2+-channel**

* ataxia is symptom in **mitochondrial multisystem disorders**.

# NONHEREDITARY ATAXIAS

**I. Idiopathic cerebellar ataxia (IDCA)**

* 1. with pure cerebellar syndrome (IDCA-C)
  2. with multiple system atrophy (IDCA-P/MSA)

**II. Symptomatic ataxias**

1. **alcoholism** (alcoholic cerebellar degeneration) → subacute cerebellar degeneration of vermis
2. **malignancy**:
   * + 1. direct mass effect in posterior fossa
       2. paraneoplastic cerebellar degeneration - autoantibodies (Yo, Ri, PCD); principally vermis.
3. **toxins** (cytotoxic drugs, antiepileptics, diphenylhydantoin, lithium, solvents, methyl mercury)
4. **metabolic** - malabsorption (acquired vitamin E deficiency), hypothyroidism
5. **physical causes** (heat stroke, hyperthermia)
6. **trauma**
7. **infections** (AIDS, syphilis, Lyme disease, Creutzfeldt-Jakob disease), cerebellar abscess
8. **demyelination** (multiple sclerosis, AIDS-related progressive multifocal leukoencephalopathy) → focal cerebellar signs
9. **vascular** → acute ataxic syndrome

Autosomal Recessive Hereditary Ataxias

Friedreich's Ataxia

- ½ of all hereditary ataxias.

- most common progressive inherited ataxia in children.

Prevalence 0.4-4.7 per 100,000 (male = female).

Genetics

9q13-21 (gene X25 coding mitochondrial protein **frataxin**):

* + - * unstable **GAA repeat expansion** in first intron;
      * few patients have **point mutations**.
* patients have undetectable (or extremely low) levels of mRNA transcribed from X25 - *reduced frataxin levels* are primary cause of neurodegeneration.
* normal length of GAA repeat is 7-22 copies.
* patients have 200-900 copies.
* disease severity correlates with number of copies.
* Friedreich's ataxia is unique among trinucleotide repeat disorders - it is autosomal recessive disorder with *no anticipation*.

Risk calculation:

**carrier frequency** is 1 in 100.

**families with one affected child** - each of remaining children carries risk of 25%.

**unaffected sibling of patient + nonconsanguineous spouse** - children have 1:1000 risk.

* because parents are asymptomatic, *consanguinity rate is high* (ranging 5.6-28% in different populations).

Pathology

Central & peripheral nervous systems + many other organs.

**Spinal cord** is thinner than normal:

1. loss of large sensory neurons in ***dorsal root ganglia*** - first pathological change!
2. neurons are also lost in ***thoracic Clarke nucleus*** (→ dorsal spinocerebellar tract).
3. degeneration & sclerosis of ***spinal tracts*** (spinocerebellar tracts, posterior columns, pyramidal tract)

**Peripheral nerves** - axonal sensory and motor ***neuropathies*** (loss of ***large myelinated axons***);

* density of ***small myelinated fibers*** is normal, but axonal size and myelin thickness are diminished.

Minor cell loss in **brain stem, cerebellum, cerebrum**!

* + - * only occasional (!) involvement of *cerebellum* (loss of Purkinje cells and moderate cerebellar atrophy).
      * mild degenerative changes of *pontine & medullary nuclei*, *optic tracts*.
      * cerebral cortex is histologically normal (except for loss of *Betz cells in precentral gyri*).

**Cardiac** pathology:

* *myocytic* hypertrophy and chronic interstitial fibrosis; myocytopathy with unusual pleomorphic nuclei.
* focal *vascular* fibromuscular dysplasia with subintimal or medial deposition of PAS-positive material.
* focal degeneration of myelinated and unmyelinated *nerves* and *cardiac ganglia*.

**Skeletal** pathology.

Clinical Features

* + early onset - before age 25 years (most often 10-15 years).

Nervous System

Four diagnostic criteria:

* + 1. **progressive ataxia of gait and stance** with onset before age 25 yrs. - first manifestation!
       - ataxia is **proprioreceptive (spinal)** ± cerebellar
       - within few years, ataxia appears in arms and then trunk.
    2. **areflexia of lower limbs**;
       - later in arms.
    3. **impaired vibration & position sense in lower limbs**;
       - later appears in arms and then trunk (→ confinement to bed).
    4. cerebellar **dysarthria** within 5 years of ataxia onset.

Atypical cases exist (diagnosis – only by genetic testing) - late-onset (after 25 yrs), retained tendon reflexes.

Other features:

* + 1. **pyramidal tract dysfunction** - extensor plantar responses!!!, progressive weakness of extremities (distal > proximal), but muscle tone is normal or decreased; distal atrophy is common in late stages.
    2. **oculomotor disturbances** (typically, fixation instability with square wave jerks and reduced gain of vestibulo-ocular reflex; nystagmus in 25%).
    3. only 10% have impaired appreciation of pain, temperature, light touch (i.e. anterolateral system is preserved).
    4. in later stages - optic atrophy (25%), progressive sensorineural hearing loss.
       - bladder function is usually unimpaired.
       - no cognitive impairment.

N.B. disease is not incompatible with *high degree of intellectual development*!

Other Systems

1. **hypertrophic obstructive cardiomyopathy**!!! (75-90%)
2. **skeletal deformities** – scoliosis (> 75%), pes cavus (> 50%)
3. **diabetes mellitus** (10-20%)

Diagnosis

**Nerve conduction studies** - ***sensory axonal neuropathy*** (sensory nerve action potentials absent in < 90% patients); normal motor nerve conduction velocity.

**Motor evoked potentials** (to transcranial magnetic stimulation) - ***pyramidal tract dysfunction*** (loss of response or increased central motor conduction time).

**Somatosensory evoked potentials** - always abnormal.

**Brain stem auditory evoked potentials** - often abnormal (pathological conduction along central auditory pathways).

**Visual evoked potentials** - abnormal in 2/3 (absence or increased latency of P100 responses).

**MRI** (imaging method of choice) - severe atrophy of cervical spinal cord + little cerebellar or brain stem atrophy.

**Molecular diagnosis** (by polymerase chain reaction).

* gene tracking with DNA markers is available for *prenatal diagnosis*.

**ECG** - T-wave inversion + ST segment changes.

**Echocardiography** - interventricular septal, left ventricular wall hypertrophy, ↓dimensions of left ventricle.

Differential diagnosis

**Hereditary motor-sensory neuropathies (HMSN)** → **motor nerve conduction velocity**:

normal - Friedreich’s ataxia

↓ - HMSN type I

normal - HMSN type II → **genetic testing**

**Refsum's disease** → serum [**phytanic acid**].

**Ataxia with isolated vitamin E deficiency** (clinically indistinguishable from Friedreich's ataxia) → serum [**vitamin E**].

**Abetalipoproteinemia** → **lipid electrophoresis**.

**GM2 –gangliosidosis**

**Adrenoleukodystrophy**

**Mitochondrial encephalomyopathies** → CSF **lactate** levels, muscle and skin **biopsy**.

### Roussy-Levy disease

- combination of HMSN type I and Friedreich ataxia.

Treatment

No specific treatment - management remains **symptomatic & palliative**.

* *physical therapy* is recommended.
* cardiomyopathy rarely requires medical treatment.

Prognosis

**Wheelchair-bound** – after 10-12 years.

Average age at death is 35-37 years (infection or heart failure).

Women have significantly better prognosis! (100% 20-year survival versus only 63% in men).

Early-Onset Cerebellar Ataxia With Retained Tendon Reflexes

- asFriedreich’s ataxia with retained tendon reflexes.

* molecular genetic basis is unknown.
* major pathological / neuroimaging abnormality - ***diffuse cerebellar atrophy*** (vs. Friedreich’s ataxia – spinal cord atrophy).
* prevalence 0.5-2.3 per 100,000.
* average disease onset - 17 years; progresses more slowly than Friedreich’s ataxia!
* clinical features:
  1. **progressive cerebellar syndrome** (wheelchair-bound only ≈ 20-25 years after onset)
  2. impaired vibration or position sense (50% patients).
  3. other noncerebellar symptoms are rare or absent (no cardiomyopathy!)

**Differential Diagnosis** - early-onset cerebellar ataxias with additional features:

1. *hypogonadism* (**Holmes syndrome**)
2. *optic atrophy and spasticity* (**Behr syndrome**)
3. *cataract, mental retardation, short stature,* *multiple skeletal abnormalities, hypogonadotropic hypogonadism* (**Marinesco-Sjögren syndrome**) - likely lysosomal storage disorder.
4. *retinal degeneration and deafness* (**Hallgren syndrome**)
5. *spasticity, amyotrophy, and bladder dysfunction* (**autosomal recessive spastic ataxia Charlevoix-Saguenay**)
6. *myoclonus* (**Ramsay Hunt syndrome**).

N.B. Ramsay Hunt syndrome has etiologic heterogeneity:

1. most common cause - mitochondrial encephalomyopathy of *myoclonic epilepsy and ragged red fibers* (MERRF).
2. *sialidosis*
3. *Baltic myoclonus (Unverricht-Lundborg disease) -* autosomal recessive disorder, mapped to chromosome 21.

Congenital Ataxias

**-** due to **cerebellar malformations**:

1. as part of complex malformation syndromes
2. limited to cerebellum.

* ***sporadic cases*** >> *familial cases* (may be inherited in autosomal recessive manner).
* variety of **exogenous factors** (toxins, viral infection, hypoxia, irradiation) may lead to cerebellar malformations.
* in some cases of severe cerebellar malformation, ataxia is surprisingly mild.
* epidemiology - rare condition (precise epidemiologic information is not available).

Clinical Features

Nonprogressive benign early-onset ataxias

N.B. children with normal intelligence can *compensate for cerebellar defects* particularly well!

**Cerebellar aplasia** (complete or near complete absence of cerebellum) - extremely rare condition.

* most cases represent secondary disruptions of normal development (primarily on vascular basis).
* seldom occurs alone.
* ***profoundly impaired motor development*** and ***persistent motor deficits*** (hypotonia, ataxia, titubations, irregularities of speech rhythm, nystagmus, etc).

N.B. there are reports of subtotal cerebellar aplasia when patients learned to stand, walk, and run.

* life expectancy ranges few weeks ÷ normal life span.

**Vermian aplasia**

* cerebellar hemispheres lie closely opposed without intervening vermis.
* associated with reduction in cerebellar hemispheres size + anomalies of cerebellar and olivary nuclei.
* clinical picture: nonprogressive cerebellar syndrome ÷ completely asymptomatic.
* life expectancy ranges few weeks ÷ normal life span.

**Joubert syndrome** - autosomal recessive agenesis of cerebellar vermis (+ changes in cerebellar cortex and dentate nucleus); no cystic dilatation in posterior fossa!

* 1. **ataxia**
  2. **abnormalities of respiratory rate control** in infancy (episodic tachypnea or prolonged apnea) – do overnight sleep study; respiratory abnormalities usually improve after infancy (if life-threatening apneic periods occur – use home ventilation).
  3. rhythmical tongue protrusion
  4. abnormal eye movements, chorioretinal colobomata
  5. mental retardation.
* most patients die before age of 3 years.

**Dandy-Walker malformation** - partial or complete aplasia of vermis + large posterior fossa cyst + other abnormalities. [see p. Dev 7 >>](http://www.neurosurgeryresident.net/Dev.%20Developmental%20anomalies\Dev7.%20Brain%20Anomalies.pdf)

* congenital ataxia is not typical feature!

**Cerebellar hypoplasia** - reduced size of entire cerebellum (or parts of it).

* neurologically healthy individuals ÷ congenital ataxia.

**Chiari malformations** - caudal herniation of parts of cerebellum and brain stem into upper cervical canal. [see p. Dev 7 >>](http://www.neurosurgeryresident.net/Dev.%20Developmental%20anomalies\Dev7.%20Brain%20Anomalies.pdf)

* do not lead to congenital ataxia!

Diagnosis

**MRI** clearly shows size of cerebellum.

Electrophysiological investigations do not reveal consistent abnormalities.

Ataxia-Telangiectasia

etiology – *autosomal recessive* single mendelian locus on 11q22.3-q23.1 - *ATM* gene (encodes protein with homology to phosphoinositol 3-kinases) - pivotal role in cellular response to DNA double-strand breaks by inducing either DNA repair or apoptotic cell death

* defective ATM protein → **cells with DNA double-strand breaks continue to proliferate** → neurodegeneration, immune system dysfunction, sensitivity to ionizing radiation, malignancies.

prevalence 1-2.5 to 100,000 births (males = females).

pathology:

* loss of Purkinje and granule cells.
* cells show bizarre enlargement of nucleus (2-5 times normal size) - **amphicytes**.
* degeneration of dorsal columns, spinocerebellar tracts, anterior horn cells.
* peripheral axonal neuropathy.

Clinical Features

ataxia + telangiectasias + immunodeficiency

1. **Progressive** **cerebellar** **degeneration** (incl. truncal ataxia, dysarthria, nystagmus, oculomotor apraxia)

* manifests shortly after child begins to walk.
* absent Romberg sign.
* mild mental retardation.
* characteristic facies – hypomimia, relaxed, dull, sad, and inattentive when unstimulated.
* wheelchair-bound by 10-15 years of age.

|  |  |
| --- | --- |
| 1. **Telangiectasias** - bulbar conjunctivae, malar eminences, ear lobes, upper neck, antecubital and popliteal spaces.  * venous origin; not symptomatic. * *appear later than ataxia* (typically at 3-6 years of age). * steadily progress and spread in symmetrical pattern. | D:\Viktoro\Neuroscience\Mov. Movement disorders, Ataxias\00. Pictures\Ataxia-telangiectasia (conjunctivae).jpg |



[Source of picture: H. Richard Winn “Youmans Neurological Surgery”, 6th ed. (2011); Saunders; ISBN-13: 978-1416053163 >>](http://www.amazon.com/gp/product/1416053166)

1. **Combined (T & B cell) immunodeficiency** (absent thymus, IgA↓, lymphopenia):

[see p. 1673 (3) >>](HTTP://WWW.NEUROSURGERYRESIDENT.NET/USMLE%202/Immunology%20(1650-1700)/1673_(3).jpg)

1. ***sinopulmonary infections*** (→ bronchiectasis, pulmonary fibrosis)
2. ***malignancies*** (10-20% patients) – esp. lymphomas, leukemias.

N.B. gene carriers (frequency in population 1%) also have increased risk of cancer (specifically breast cancer)!

1. **CNS tumors** (astrocytoma, medulloblastoma\*, craniopharyngioma, meningiomas)

\*recent evidence does not, however, suggest primary role for ATM gene in oncogenesis of medulloblastoma

* extreme sensitivity of AT patients to ionizing radiation necessitates lower than standard dose regimens perhaps optimizing balance between maximizing effectiveness and minimizing risk.

1. **Skin pathology** - progeric changes, hyperpigmentation / hypopigmentation with cutaneous atrophy, seborrheic dermatitis.
2. **Endocrine abnormalities** – dwarfing, hypogonadism (esp. female), unusual type of diabetes mellitus.

Diagnosis

* ↑ serum [**α-fetoprotein**] and plasma [**carcinoembryonic antigen**] - typical, but not invariable, so not required for diagnosis.
* ↓ IgA, IgG2, and IgE.
* **CT / MRI** - ***cerebellar atrophy***.

Prenatal diagnosis:

* 1. [α-fetoprotein] in amniotic fluid.
  2. increased spontaneous (or radiation induced) chromosomal breakage of amniotic cell DNA.
  3. ATM protein dysfunction on molecular diagnostic testing

Prognosis

* ***homozygotes*** exhibit drastically shortened life spans (50% dye before age of 20)
* ***heterozygotes*** live 7-8 years less than their noncarrier counterparts and suffer from early cancers and ischemic heart disease.

Ataxia due to vit. E deficiency

Etiology - vitamin E deficiency in nervous system due to **abnormalities in interactions of vit. E with VLDL**:

VLDL is transport molecule for vitamin E

1. **abetalipoproteinemia (Bassen-Kornzweig syndrome)** - mutation in gene for **microsomal triglyceride transfer protein (MTP)** → *impaired formation and secretion of VLDL* in liver → deficient delivery of vit. E to tissues. [see p. 789 >>](http://www.neurosurgeryresident.net/USMLE%202\Biochemistry,%20Metabolic%20Disorders%20(501-900)\789.jpg)
2. **ataxia with isolated vitamin E deficiency (AVED)** - 8q13 mutation in gene for **α-tocopherol transport protein (α-TTP)** → *impaired binding of vit. E to VLDL* → vit. E deficiency in tissues; clinically indistinguishable from classic Friedreich's ataxia.

Diagnosis - serum [vitamin E], lipid electrophoresis.

Autosomal Dominant Hereditary Ataxias

- generally begin during adult years.

Spinocerebellar Ataxia Type 1

prevalence 1.2 in 100,000 (large regional variations due to founder effects).

Etiopathogenesis

6p21.3 (**unstable CAG repeat expansion** within translated region of gene for protein **ataxin-1**):

* normal repeat length 6-39 trinucleotides; normal alleles have midstream CAT interruption.
* patients have one allele with 40-81 uninterrupted CAG stretches;
  + tendency to expand further during ***meiosis***, particularly during spermatogenesis (larger expansions in offspring of affected males);
  + ***mitotic*** instability also occurs (varying repeat lengths in different body tissues).
  + inverse correlation between CAG repeat length and age of onset → anticipation.
* physiological function of ataxin-1 is unknown.
* normal **ataxin-1** and its mutated form are expressed ubiquitously within body at comparable levels.
* pathogenetic mechanism is not loss of physiological function of **ataxin-1** but rather *gain of new toxic function*.

Neuropathology – ***olivopontocerebellar atrophy*** + degeneration of ***ascending spinal pathways*** + minor degeneration of pyramidal tract.

Clinical Features

* onset - any time from adolescence to late adulthood (with features of anticipation); average - 35 yr.
* wheelchair-bound ≈ 10-13 years after onset.
* median survival 18-20 years after onset (usually pneumonia).

1. **Progressive cerebellar syndrome**
2. **Additional noncerebellar symptoms**:
   1. ***pyramidal tract signs***
   2. ***skeletal muscle atrophy***
   3. ***pale optic discs*** (no retinal degeneration!).
   4. ***dysphagia*** is typical at late stages.
   5. less frequent symptoms - gaze palsy, slow saccades, decreased vibration sense, bladder dysfunction
   6. rare symptoms - basal ganglia symptoms, dementia.

Clinically, SCA1 cannot be distinguished with certainty from other forms of ADCA-I.

Diagnosis

Diagnosis is by **genetic analysis**.

**MRI** - diffuse ***cerebellar*** atrophy, ***brain stem*** atrophy, ***cervical spinal cord*** atrophy.

**SNAPs** reduced in almost all patients - sensory axonal neuropathy.

**MEPs** abnormal in almost all patients (loss of responses or increased CMCT indicates pyramidal tract involvement).

**SEPs** - delayed or absent.

**VEPs** - loss or delay of P100 - in almost all patients.

**BAEPs** - delays in peaks I, III, V and increased interpeak latencies - in ½ patients.

Spinocerebellar Ataxia Type 2

Prevalence unknown.

* large regional variations due to founder effects (esp. high prevalence in Holguin province of Cuba).

Etiopathogenesis

12q23-24.1 (**CAG repeat expansion** - gene for protein **ataxin-2**).

* expanded alleles have 35-39 repeats.

Neuropathology – ***olivopontocerebellar atrophy*** + degeneration of ***posterior columns*** and ***spinocerebellar pathways*** + cell loss in ***substantia nigra***

Clinical Features

* 1. Progressive cerebellar syndrome (***saccade slowing*** is highly characteristic feature).
  2. Absent tendon reflexes.
  3. Vibration sense decreased.
  4. Vertical or horizontal gaze palsy (50%).
* **onset** - any time from early childhood to late adulthood (with anticipation); average - 35 years.
* wheelchair-bound ≈ 15 years after onset.
* median survival 25 years after onset.

Clinically cannot be distinguished with certainty from other forms of ADCA-I.

Diagnosis

* diagnosis is by **genetic analysis**.
* **MRI** - severe ***olivopontocerebellar*** atrophy + ***cervical spinal cord*** atrophy (in most patients).
* **electrophysiology** ≈ SCA1 (but MEPs are usually normal).

Spinocerebellar Ataxia Type 3 (Machado-Joseph Disease)

- **autosomal dominant** form of striatonigral degeneration. [see p. Mov12 >>](http://www.neurosurgeryresident.net/Mov.%20Movement%20disorders,%20Ataxias\Mov12.%20Hypokinetic%20Disorders%203%20(Parkinsonism-Plus).pdf)

prevalence 1.2 in 100,000 (large regional variations due to founder effects).

* most patients are of *Azorean*-*Portuguese ancestry*.

Etiopathogenesis

14q32.1 (unstable **CAG repeat expansion** - gene for protein **ataxin-3**).

* normal length 14-40 trinucleotides.

patients have one allele with 62-200 repeat units.

* inverse correlation between CAG repeat length and age of onset.
* mitotic and meiotic instability (anticipation without paternal effect).

Neuropathology - similar to striatonigral degeneration + degeneration of ***spinocerebellar tracts***, ***vestibular nuclei***, ***dentate nucleus***.

N.B. cerebellar cortex and inferior olives are spared!

Clinical Features

* onset between early childhood and late adulthood (with anticipation); average – 25-40 yrs.
* wheelchair-bound ≈ 15 years after onset.
* median survival 25-30 years after onset.

1. **Progressive cerebellar syndrome**
2. **Supranuclear ophthalmoparesis** (spares down gaze until late stages); lid retraction and decreased blinking (“ bulging” eyes) in 33% patients.
3. In repeat lengths > 74 - *pyramidal tract involvement* (spasticity, hyperreflexia, extensor plantar responses), *mild parkinsonism*.

* sometimes, peripheral neuropathy, dystonia (suggestive for SAC3 among other ADCA-I).
* cognitive function preserved!

Clinically, cannot be distinguished with certainty from other forms of ADCA-I.

*Very great phenotypic variation* (clinical subclasses have been formulated but not recommended):

**type I MJD** (amyotrophic lateral sclerosis-parkinsonism-dystonia type) – early onset (mean age, 24 years); slow and stiff gait, facial fasciculations, facial myokymia.

**type II MJD** (ataxic type) – most common form - mean age, 40 years; true cerebellar deficits.

**type III MJD** (ataxic-amyotrophic type) - mean age, 47 years; slower ataxia progression; prominent peripheral signs (distal sensory loss, distal atrophy); no corticospinal or extrapyramidal findings.

Diagnosis

Diagnosis is by **genetic analysis**.

**MRI** - ***atrophic cervical spinal cord***! (as in SCA1, 2); absence of cerebellar and brain stem atrophy!

**Electrophysiology** ≈ SCA2.

Spinocerebellar Ataxia Type 4

ADCA-I mapped to 16q24-ter.

* one family described.
* clinical features - progressive **ataxia**, **pyramidal tract** deficits, prominent **sensory axonal neuropathy**.
* normal eye movements.

Spinocerebellar Ataxia Type 5

ADCA-III mapped to 11cen (*gene has not yet been cloned*, mutation unknown).

* described in single American family (descended from paternal grandparents of President Abraham Lincoln).
* clinical features - **pure cerebellar syndrome (ADCA-III)**
  + onset at any time between childhood and late adulthood with features of anticipation (esp. with maternal transmission); average - 30 years.
  + slower rate of progression than other ADCA - life expectancy is not shortened!
* genetic test is not available (only **linkage analysis** with markers closely linked to SCA5 locus).
* **MRI** - ***cerebellar atrophy*** with no brain stem involvement.

Spinocerebellar Ataxia Type 6

ADCA-III mapped to l9p13.1 (small\* **CAG repeat expansion** - in gene for **alpha1A voltage-dependent Ca2+-channel** subunit, i.e. SCA6 is channelopathy).

\*normal number 4-16; in patients 21-27

* clinical features - **pure cerebellar syndrome (ADCA-III)**

Spinocerebellar Ataxia Type 7

ADCA-II mapped to 3p14-21.1 (**CAG repeat expansion** - gene for **ataxin-7**).

* marked anticipation in ADCA-II families.
* neuropathology – OPCA, primarily macular degeneration (spreads to involve retina → secondary optic nerve atrophy).
* clinical features - **cerebellar syndrome + retinal degeneration** **(ADCA-II)**
  + onset at any time between childhood and late adulthood with features of anticipation (esp. with paternal transmission); average - 25 years.
  + survival: children die after ≈ 5 years; adult patients survive for ≈ 15 years.
* diagnosis - **linkage** to SCA7 locus; **MRI** – OPCA (cerebellar and brain stem atrophy).

Dentatorubral-Pallidoluysian Atrophy

12p12.3-13.1 (unstable **CAG repeat expansion** - gene for **atrophin** - protein of unknown function).

* normal repeat length 7-23 trinucleotides, in patients – 49-79 repeat units.
* occurs mainly in Japan (prevalence - 0.1 per 100,000); sporadic mutations also occur.
* neuropathology - degenerative changes in:
  1. ***dentate nucleus*** with its projection to ***red nucleus***
  2. ***external pallidum*** with its projection to ***subthalamic nucleus (of Luys)***.
* clinical features - **cerebellar syndrome +** progressive **dementia**!!! + additional features:
  + 1. if onset < 21 years - progressive **myoclonus epilepsy**.
    2. later disease onset - **choreic / dystonic** movements, **psychiatric** abnormalities.
  + onset at any time between childhood and late adulthood with features of anticipation (esp. with paternal transmission); average - 30 years.
* **EEG** - slowed background activity (80%), epileptiform EEG patterns (50%), photosensitivity (30%).
* **MRI** - atrophy of ***superior cerebellar peduncles***, high-intensity signals in ***pallidum*** (on T2-weighted images).
* avoid phenytoin in treatment of epilepsy (may worsen ataxia).

Episodic Ataxias

Episodic ataxia type 1

* rare autosomal dominant missense mutation in 12p - gene KCNA1 (**K+ channel**)
* *inefficient nerve cell repolarization* after action potential.

clinical features

* onset in early childhood.
* brief attacks of **ataxia & dysarthria**:
  + last for seconds to minutes;
  + occur several times per day - provoked by movements and startle.
  + **favorable prognosis** - attacks tend to abate after early childhood.
* interictal myokymia around eyes, in hands.

diagnosis

* molecular genetic test is not available.
* MRI is normal.

treatment

**Acetazolamide** (250 mg ×2/d) - reduces attacks in some but not all kindreds.

**Anticonvulsants** - to reduce myokymia.

Episodic ataxia type 2

* rare autosomal dominant ***mutation***\* in l9p13.1 - gene for **α1A voltage-dependent Ca2+-channel** subunit.

\****CAG repeat*** ***expansion*** of same gene causes SCA6.

clinical features

* onset at 6 weeks ÷ 30 years of age.
* attacks of **ataxia & dysarthria**:
  + last for several hours ÷ days;
  + occur several times per day ÷ less than once month;
  + provoked by stress, exercise, fatigue (but not movements or startle!).
* interictal mild ataxia (may be progressing!) and gaze-evoked nystagmus.
* **MRI** - atrophy of ***cerebellar vermis***.

treatment

Continuous **acetazolamide** (250 mg ×2/d) - completely abolishes attacks (as long as drug is used).

Nonhereditary, Idiopathic Cerebellar Ataxia

**-** heterogeneous group of degenerative ataxias with **late-onset** (after 25 years; average – 55 yrs\*).

\*later than ADCA

* etiology unknown - major progress in understanding pathogenesis is not expected in near future.

Cerebellar type (IDCA-C)

- exclusive degeneration of ***cerebellar cortex*** → progressive purely cerebellar syndrome.

* MRI - pure *cerebellar* atrophy (esp. in vermis) without brain stem or spinal cord involvement.
* almost normal life expectancy!!!

Plus type (IDCA-P)

- part of spectrum of **multiple system atrophy (MSA)**: [see p. Mov12 >>](http://www.neurosurgeryresident.net/Mov.%20Movement%20disorders,%20Ataxias\Mov12.%20Hypokinetic%20Disorders%203%20(Parkinsonism-Plus).pdf)

* + - MSA-typical oligodendroglial argyrophilic intracytoplasmic *inclusion bodies*.
    - various degenerations - ***olivopontocerebellar***, ***striatonigral***, ***intermediolateral spinal columns***, ***Onuf's nucleus***, ***pyramidal tracts*** → IDCA-C + additional clinical features.
* *prognosis is poor*: wheelchair-bound after ≈ 5 yrs, median survival 8-10 years
* MRI - diffuse atrophy of *cerebellum*, *middle cerebellar peduncles*, *basis pontis*.

N.B. normal size of cervical spinal cord (vs. ADCA)

T2-weighted **MRI** of IDCA-P

**A**. **Hypointensities of basal ganglia**.

*Upper left*: normal.

*Upper right*: hypointensity at dorsolateral margin of putamen (IDCA-P beginning).

*Lower left*: strong hypointensity extending through part of body of putamen.

*Lower right*: hypointensity extending throughout putamen, with intensity exceeding that in globus pallidus (late-stage IDCA-P); hyperintensity at lateral putaminal border.

Goetz figure 35-3

[Source of picture: Christopher G. Goetz “Textbook of Clinical Neurology” (1999); W.B. Saunders Company; ISBN 0-7216-6423-7 >>](http://www.amazon.com/gp/product/1416036180)

**B**. **Hyperintensities** (degeneration and gliosis) in:

**transverse pontine fibers** between tegmentum and base of pons (*left side*);

**middle cerebellar peduncles** (*right side*).

*Upper panel*: normal. *Lower panel*: IDCA-P/MSA.

Acute Cerebellar Ataxia

1. **Acute viral cerebellitis** (CSF as in acute viral infection).
2. **Postinfection immunologic syndrome**

* primarily in children 1-3 yr.
* 2-3 wk after viral illness (varicella-zoster, Coxsackie, echovirus) - autoimmune response to viral agent affecting cerebellum.
* onset is sudden – **pancerebellar syndrome**:
  + truncal ataxia can be so severe that child is unable to stand or sit.
  + impressive dysarthria
  + horizontal nystagmus (50%).
  + fever and nuchal rigidity are absent.
* diagnosis by exclusion.
* CSF - normal or slight pleocytosis (10-30 lymphocytes /mm3) → moderate protein elevation.
* ataxia begins to improve in few weeks (may persist for as long as 2 months).
* *prognosis for complete recovery is excellent* (small number have long-term sequelae - behavioral and speech disorders, ataxia).

Bibliography for ch. “Movement disorders, Ataxias” → follow this [link >>](http://www.neurosurgeryresident.net/Mov.%20Movement%20disorders,%20Ataxias\Mov.%20Bibliography.pdf)

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