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
   2) **with pure cerebellar syndrome (ADCA-III)**
      SCA5 - 11cen (mutation and gene unknown)
      SCA6 - l9p13.1 (CAG repeat expansion – gene for **α_{1A} voltage-dependent Ca^{2+} channel**)
2. **With retinal degeneration (ADCA-II)**
   SCA7 - 3p14-21.1 (CAG repeat expansion – gene for **ataxin-7**)
3. **Dentatorubral-pallidoluysian atrophy** - 12p12.3-13.1 (CAG repeat expansion; gene for **atrophin**)
4. **Episodic ataxias (EA)**
   EA-1 - 12p (mutation – gene for **K^+ channel**)
   EA-2 - l9p13.1 (mutation – gene for **α_{1A} voltage-dependent Ca^{2+}-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**:
   a) direct mass effect in posterior fossa
   b) 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:
5) **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.
6) **oculomotor disturbances** (typically, fixation instability with square wave jerks and reduced gain of vestibulo-ocular reflex; nystagmus in 25%).
7) only 10% have impaired appreciation of pain, temperature, light touch (i.e. anterolateral system is preserved).
8) 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**.
GM_2 –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

- as Friedreich'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:
a) *hypogonadism* (**HOLMES syndrome**)
b) *optic atrophy and spasticity* (**BEHR syndrome**)
c) *cataract, mental retardation, short stature, multiple skeletal abnormalities, hypogonadotropic hypogonadism* (**MARINESCO-SJÖGREN syndrome**) - likely lysosomal storage disorder.
d) *retinal degeneration and deafness* (**HALLGREN syndrome**)
e) *spasticity, amyotrophy, and bladder dysfunction* (**autosomal recessive spastic ataxia CHARLEVOIX-SAGUENAY**)
f) *myoclonus* (**RAMSAY HUNT syndrome**).
N.B. Ramsay Hunt syndrome has etiologic heterogeneity:
a) most common cause - mitochondrial encephalomyopathy of *myoclonic epilepsy and ragged red fibers* (MERRF).
b) *sialidosis*
c) *Baltic myoclonus (Unverricht-Lundborg disease)* - autosomal recessive disorder, mapped to chromosome 21.

CONGENITAL ATAXIAS

- due to **CEREBELLAR MALFORMATIONS**:
  a) as part of complex malformation syndromes
  b) 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 >>

- 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 >>

- 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).

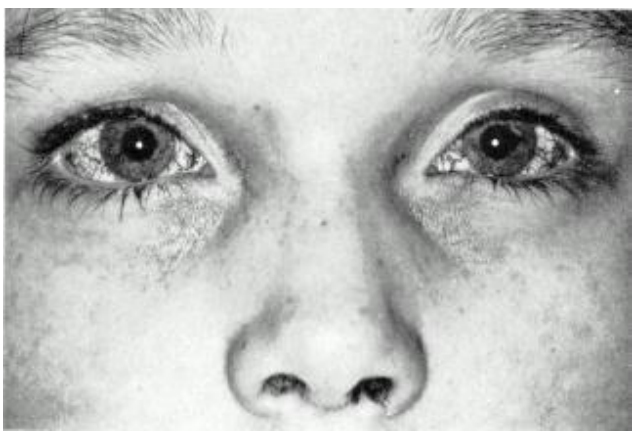
PATHOLOGY:

- 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.

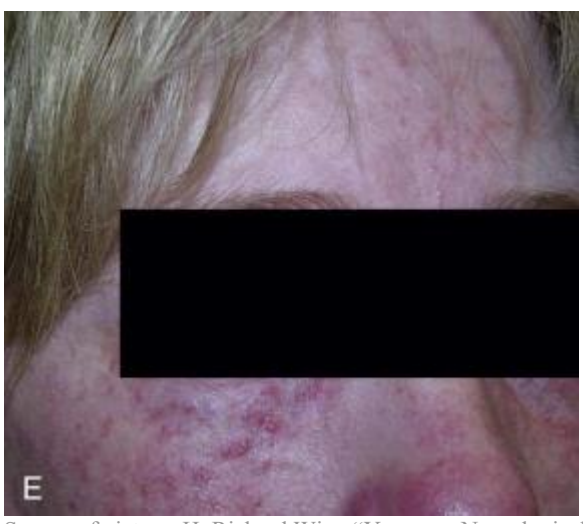
CLINICAL FEATURES

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.



2. **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.



Source of picture: H. Richard Winn "Youmans Neurological Surgery", 6th ed. (2011); Saunders; ISBN-13: 978-1416053163 >>

3. **Combined (T & B cell) immunodeficiency** (absent thymus, IgA↓, lymphopenia): see p. 1673 (3) >>
   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)!
4. **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.

5. **Skin pathology** - progeric changes, hyperpigmentation / hypopigmentation with cutaneous atrophy, seborrheic dermatitis.
6. **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

A) **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 >>

B) **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 >>

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 **alpha$_{1A}$ voltage-dependent Ca^{2+}-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:
  a) if onset < 21 years - progressive **myoclonus epilepsy**.
  b) 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 **α_{1A} voltage-dependent Ca^{2+}-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!!!

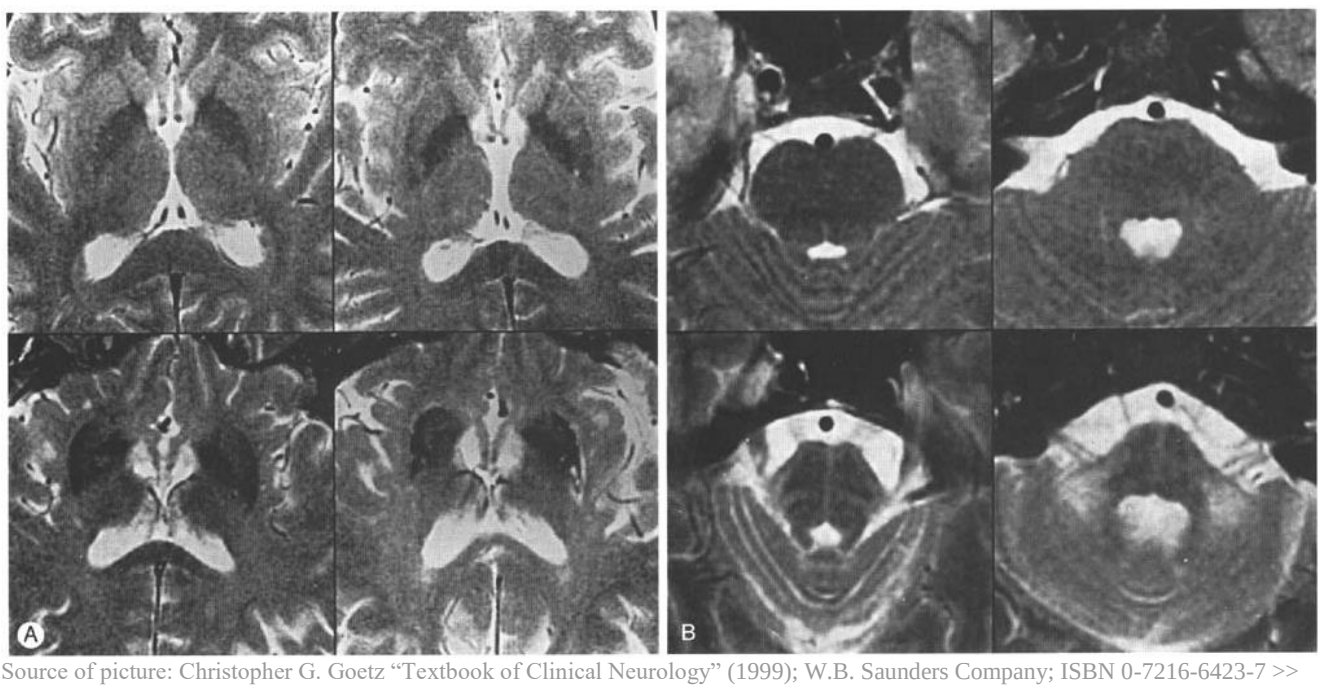
PLUS TYPE (IDCA-P)

- part of spectrum of **multiple system atrophy (MSA)**: see p. Mov12 >>
  - 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.



Source of picture: Christopher G. Goetz "Textbook of Clinical Neurology" (1999); W.B. Saunders Company; ISBN 0-7216-6423-7 >>

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 /mm^3) → 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 >>