**Ataxias**

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**AUTOSOMAL RECESSIVE HEREDITARY ATAXIAS**

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4. Ataxia-telangiectasia - 11q22.2-23 (gene ATM)
5. Ataxias due to vitamin E deficiency - 8q (gene for u- tocopherol transport protein)

**ACUTE CEREBELLAR ATAXIA**

1. Ataxia - wide spectrum of disorders
   - slowly progressive ataxia that usually begins in legs is leading symptom
   - pathologica bultmark - degeneration / malformation of cerebellum and/or its related structures (e.g. brain stem, spinal pathways)
   - additional lesions elsewhere frequently are present (exp. peripheral neuropathies)
   - no specific treatment!
     - trials with 5-HYDROXYTryptophan, Amantadine, Buspiron may be attempted, although no controlled trials clearly demonstrate efficacy.
     - physical therapy!

**CLASSIFICATION OF ATAXIAS**

**Hereditary Ataxias**

Clinical classification introduced by Harding (1983):

**I. AUTOSOMAL RECESSIVE ATAXIAS** - early-onset ataxias.

1. Friedreich's ataxia - 9q13 (mitochondrial gene for ataxias)
2. Early-onset cerebellar ataxias with retained tendon reflexes
3. Congenital ataxias (due to cerebellar malformations)
4. Ataxia-telangiectasia - 11q22.2-23 (gene ATM)
5. Ataxias due to vitamin E deficiency - 8q (gene for u-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 - 12q24.1 (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 - 9p13.1 (CAG repeat expansion - gene for a voltage-dependent Ca\(^{2+}\) channel)

2. With retinal degeneration (ADCA-II)
   - SCA7 - 3p14.2-21.1 (CAG repeat expansion - gene for ataxin-7)
   - Denticulorubral-pallidoluysian atrophy - 12p12.3-13.1 (CAG repeat expansion; gene for atrophin)

3. Episodic ataxias (EA)
   - EA1 - 12p (mutation - gene for K\(^{+}\) channel)
   - EA2 - 9p13.1 (mutation - gene for \(\alpha\)-voltage-dependent Ca\(^{2+}\) channel)

   Ataxia is symptom in mitochondrial multisystem disorders.

**Non-hereditary ataxias**

1. Idiopathic cerebellar ataxia (IDCA)
   1) with pure cerebellar syndrome (IDCA-C)
   2) with multiple system atrophy (IDCA-PWSA)

2. Symptomatic ataxias:
   1) alcoholism (alcoholic cerebellar degeneration) → subacute cerebellar degeneration of vermis
   2) malignancy:
      a) direct mass effect in posterior fossa
Other features:

Other features:

Four Nervous System

- Cardiac
- Infections (AIDS, syphilis, Lyme disease, Creutzfeldt-Jakob disease), cerebellar abscess
- Demyelination (multiple sclerosis, AIDS-related progressive multifocal leukoencephalopathy) → focal cerebellar signs
- Vascular → acute atactic 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 FXS: 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 FXS - reduced frataxin levels are primary cause of neurodegeneration.
- Normal length of GAA repeat in 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.
- Carrier frequency is 1 in 100.
- Because parents are asymptomatic.
- Consanguinity rate is high (ranging 5-28% 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 gyr).

Cardiac pathology:
- Myocyte hypertrophy and chronic interstitial fibrosis; myocytolpathy 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:

Poor diagnostic criteria:

1) Progressive ataxia of gait and stance with onset before age 25 yrs - first manifestation?
- Ataxia is proprioceptive (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 - extense 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; nyctagmus in 25%).
- Only 10% have impaired appreciation of pain, temperature, light touch (i.e. anterolateral system is preserved).

7) In late 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 - sensorial 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 - often 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 cerebral 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.

Echo cardiography - 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].

Aletblaptoproteinemia → lipid electrophoresis.

GML- gangliosidosidosis

Adrenoleukodystrophy

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

ROUSSEY-JAVIS 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
- in Friedreich's ataxia with retained tendon reflexes
• molecular genetic basis is unknown.
• major pathologic/ 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?)

• other noncerebellar symptoms are rare or absent (no cardiomyopathy?)

DIFFERENTIAL DIAGNOSIS
- early-onset cerebellar ataxias with additional features:

a) hypogonadism (HOMSES syndrome)

b) optic atrophy and spasticity (BEDIE syndrome)

c) catacatax, mental retardation, short stature, multiple skeletal abnormalities, hypogonadotropic hypogonadism (MARINESCO-SJÖGREEN syndrome) - likely lysosomal storage disorder.

d) retinal degeneration and deafness (HALLEGRN syndrome)

e) spasticity, atrohypophysis, and bladder dysfunction (autosomal recessive spastic ataxia

f) myeloma (RAMAY HUNT syndrome)

N.B. Ramay Hunt syndrome has etiologic heterogeneity:

a) most common cause - mitochondrial encephalomyopathy of myelonic epilips and ragged red fibers (MERRF).

b) sialidosis

c) Baltic myeloma (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).
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 defects (hypotonia, ataxia, titubation, 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 months to normal life span.

Verminal 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 months to normal life span.

Joubert syndrome - autosomal recessive agenesis of cerebellar vermis (+ changes in cerebellar cortex and dentate nucleus); no cystic dilation 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) rhythmic 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!

Ataxia-Telangiectasia

Etiology - autosomal recessive single mendelian locus on 11q22.3-p23.1 - 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).
- degeneration of dorsal columns, spinocerebellar tracts, anterior horn cells.
- peripheral neuropathy.

Ataxia + Telangiectasia + 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 - hypotonia, relaxed, dull, sad, and inattentive when unstimulated.
- wheelchair-bound by 10-15 years of age.

2. Telangiectasia - bilateral conjunctival, malar engainances, ear lobes, upper neck, antecubital and poplital spaces.

- venous origin; not symptomatic.
- appear later than ataxia (typically at 3-6 years of age)
- steadily progress and spread in symmetrical pattern.
3. Combined (T & B cell) immunodeficiency (absent thymus, IgA, lymphopenia): see p. 1673 (3) 

1) sino-pulmonary infections (→ bronchiectasis, pulmonary fibrosis)  
2) malignancies (10-25% patients) – esp. lymphomas, leukemias.  
N.B. gene carriers (frequency in population 1%) also have increased risk of cancer (specifically breast cancer)!  

4. CNS tumour (astrocytoma, medulloblastoma*, craniopharyngioma, meningiomas) 

- extreme sensitivity of AT patients to ionizing radiation necessitates optimizing balance between maximizing effectiveness and minimizing risk.  

5. Skin pathology – progeric changes, hyperpigmentation / hypopigmentation with cutaneous atrophy, seborrhoeic 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.  

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) - Βγ3 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 classical 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 CAG interruptions;  
- patients have one allele with 40-81 uninterrupted CAG stretches;  
- tendancy to expand further during meiosis, particularly during spermatogenesis (larger expansions in offspring of affected males);  
- minile 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
1. Progressive cerebellar syndrome

2. Additional noncerebellar symptoms:
   1) pyramidal tract signs
   2) skeletal muscle atrophy
   3) pali optic discs (no retinal degeneration!).
   4) dysphagia is typical at late stages.
   5) loss frequent symptoms - gape paly, 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 - diffus spinocerebellar atrophy, brain stem atrophy, cerebellar 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, II, 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**

14q32.1

- 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 gape paly (50%).

5. **onset** - any time from early childhood to late adulthood (with anticipation); average - 35 years.

6. wheelchair-bound = 15 years after onset.

7. MEDIAN SURVIVAL 25 years after onset.

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

**Spino cerebellar Ataxia Type 3 (Machado-Joseph Disease)**

- autosomal dominant form of striatonegral 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**


- expanded alleles have 35-39 repeats.

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

**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 ophtalmoplegiaspares down gaze until late stages; lid retraction and decreased blinking (“bulging” eyes) in 33% patients.

3. In repeat lengths > 74 - pyramidal tract involvement (spasticity, hypertreflexia, 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 I, 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 cerebral spinal cord! (as in SCA1, 2), absence of cerebellar and brain stem atrophy! Electrophysiology = SCA2.

**Spinocerebellar Ataxia Type 4**

ADCA-I mapped to 16q24-mq:
- 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 11q23 (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 SCAS locus).
- MRI - cerebellar atrophy with no brain stem involvement.

**Spinocerebellar Ataxia Type 6**

ADCA-II mapped to 1p14-11 (small* CAG repeat expansion - gene for alpha2 voltage-dependent Ca2+ channel subunit, i.e. SCA6 is channelpathy):
- **CLINICAL FEATURES** - pure cerebellar syndrome (ADCA-III)
- normal repeat number 4-16, in patients 21-27 years; average 10 years.
- **NEUROPATHOLOGY** occurs mainly in Japan (PREVALENCE - 0.1 per 100,000); sporadic mutations also occur.
- **NEUROPATHOLOGY** - degenerative changes in: dentatorubral and pallidoluysian atrophy.
- **DIAGNOSIS** - linkage to SCA7 locus; MRI - OPCA (cerebellar and brain stem atrophy).

**Spinocerebellar Ataxia Type 7**

ADCA-II mapped to 1p14-22.1 (CAG repeat expansion - gene for ataxin-7):
- marked anticipation in ADCA-II families.
- **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.
- **PREVALENCE** - 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 (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:
  a) onset < 21 years - progressive myoclonus epilepsy.
  b) late 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 12q - 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.
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 in sudden – pan cerebellar 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 lymphocytes/mm³) → moderate protein elevation.
   - ataxia begins to improve in few weeks (may persist for as long as 2 mos).
   - prognosis for complete recovery is excellent (small number have long-term sequelae - behavioral and speech disorders, ataxia).

Acute cerebellar ataxia is also classifiable under the following titles:

Acute cerebellar degeneration
Acute cerebellar degeneration with disordered gait
Acute cerebellar ataxia with diplopia
Acute cerebellar degeneration with ataxia and disordered gait
Acute cerebellar ataxia with disordered gait, dysphagia, and disordered vision
Acute cerebellar ataxia with disordered gait, dysphonia, and disordered vision
Acute cerebellar ataxia with disordered gait, dysphagia, dysphonia, and disordered vision

Acute cerebellar ataxia is a condition characterized by a sudden onset of ataxia affecting the cerebellum. It can be caused by various factors, including viral infections, autoimmune responses, or other immune-mediated processes. The symptoms typically include severe truncal ataxia, dysarthria, horizontal nystagmus, and fever. The condition is generally self-limiting and resolves within a few weeks in most cases. The prognosis is excellent, with a high likelihood of complete recovery. However, some patients may experience long-term sequelae such as behavioral and speech disorders. Acute Cerebellar Ataxia is not expected in near future.