

15 Spinocerebellar Ataxias

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Introduction

The term ataxia derived from the Greek means ‘irregularity’ or ‘disorderliness’. This talk is devoted to the symptoms, signs and the pathological and clinical features of the disorders of the cerebellum (and its connections). There are two basic clinical rules which can be applied: 1) lesions of the vermis generally causes ataxia of midline structure (i.e. truncal and gait ataxia); 2) output from the cerebellar hemisphere is to the contralateral cerebral hemisphere, which provides output to the contralateral limbs, therefore cerebellar hemisphere lesions are ipsilateral.

Symptoms of Ataxic Disorders

The history is extremely important. The age and speed of onset and development of other features provides important aetiological clues. Rate of progress and any precipitating or relieving factors should be noted and of course a detailed family history is paramount. Other features which should be sought after and assessed include:

Disturbances of Gait

- Common presenting feature
- Include length of history early motor milestones etc
- Pattern of onset and progression- insidious, acute, subacute chronic
- Additional features e.g. early morning headache/vomiting (raised ICP).

Limb Inco-ordination and Tremor

- Clumsiness of arms often late and more common in M c.f. degenerative disease
- Titubation but little gait disturbance think Wilson’s disease.

Dysarthria

- Often noted by witnesses first
- Presence excludes purely sensory ataxia.

Visual and Ocular Motor Symptoms

- Rare in ‘pure’ cerebellar disease
- May suggest brain stem disease
- Oscillopsia think paraneoplastic
- Rare syndromes associated with visual loss e.g. SCA 7, NARP.

Other Symptoms

- Enquire about headache or vomiting- Think ICP post fossa mass
- Intermittent plus fever think cystercercosis
- Direct questioning should cover urinary system, skeletal deformities, cardiac disease and assessment of cognitive abilities since many ataxias can be associated with disease in other systems.
- A detailed inquiry of drug ingestion (for both medical and recreational purposes, including alcohol).

Signs of Cerebellar Disease

Gait and Posture

- Note narrow base- extrapyramidal
- Arm swing – if very ataxic some patients do not swing arms.

Speech

- Scanning dysarthria
- If additional signs such as a slow moving tongue and brisk jaw jerk consider pseudo-bulbar element.

Muscle Tone

- Hypotonia and pendular knee jerks very rare.

Limb Ataxia

- Dysmetria, dysdiadokinesis and rapid tapping all useful
- Note: There is also a natural asymmetry in cerebellar function, with better performance, particularly for rapid alternating movements, in the dominant limb. About 40% of patients with vermis lesions do not have limb ataxia but have striking gait ataxia.

Tremor

- Intention tremor is present if a rhythmical side to side oscillation is seen on finger-nose testing. A combination of gross intention tremor and a postural component is often called rubral or red nucleus tremor, although peduncular tremor is probably a more accurate label. It is most commonly seen in multiple sclerosis and occasionally in late-onset degenerative ataxias.

Eye Movements

- Square wave jerks may be seen in the primary position; these are inappropriate saccades that disrupt fixation and are followed by a corrective saccade within 200 msec.
- Saccadic pursuit, jerky pursuit, saccadic intrusion are same thing
- Remember VOR and VOR suppression.

Other Neurological Signs and General Examination

- A range of other signs may be seen in some of the rare ataxic syndromes (Table 1).

Table 1 Differential Diagnosis of Ataxic Disorders - Associated General Physical Signs

Feature	Condition	
Short stature	Mitochondrial encephalomyopathy, Ataxia telangiectasia, Sjögren-Larsson syndrome, Cockayne syndrome	
Hypogonadism	Recessive ataxia with hypogonadism, ataxia telangiectasia, Sjögren-Larsson syndrome, mitochondrial encephalomyopathy, adrenoleukomyeloneuropathy	
Skeletal deformity	Friedreich's ataxia, Sjögren-Larsson syndrome, many other early-onset inherited ataxias, hereditary motor and sensory neuropathy	
Immunodeficiency	Ataxia telangiectasia, multiple carboxylase deficiencies	
Malnutrition	Vitamin E deficiency, alcoholic cerebellar degeneration	
Hair	Argininosuccinic aciduria Giant axonal neuropathy Thallium poisoning, hypothyroidism, adrenoleukomyeloneuropathy Foramen magnum lesions	Brittle Tight curls Loss Low hairline
Skin	Ataxia telangiectasia Xeroderma pigmentosum Hartnup disease Cholestanolosis Hypothyroidism, Refsum's disease, Cockayne syndrome Adrenoleukomyeloneuropathy	Telangiectases, particularly conjunctiva, nose, ears, flexures Extreme light sensitivity, tumours Pellagra-type rash Tendinous swellings Dry skin Pigmentation
Eyes	Ataxia telangiectasia Wilson's disease Cerebellar hemangioblastoma Congenital rubella, cholestanolosis, Sjögren-Larsson syndrome Gillespie syndrome	(see Skin) Kayser-Fleischer rings Retinal angiomas in von-Hippel-Lindau disease Cataract Aniridia
Fever	Abscess, viral cerebellitis, cysticercosis, dominant periodic ataxia, intermittent metabolic ataxias. Fever may precipitate neurological deterioration in last two. Vomiting. Haemorrhage, infarction, demyelination, posterior fossa mass lesions, intermittent metabolic ataxias	
Hepatosplenomegaly	Niemann-Pick disease type C, some childhood metabolic ataxias, Wilson's disease, alcoholic cerebellar degeneration	
Heart disease	Friedreich's ataxia Mitochondrial encephalomyopathy	Cardiomegaly, murmurs, arrhythmias, late heart failure, abnormal ECG Conduction defects

Disorders of the Cerebellum

Ataxia of Acute or Subacute Onset

Cerebellar ataxia with extremely acute onset has two main causes: cerebellar haemorrhage (usually associated with headache, vertigo, vomiting, altered consciousness, and neck stiffness), and cerebellar infarction (in which cerebellar signs are usually combined with signs of brain stem ischaemia, and the presentation may mimic that of haemorrhage). Diagnosis should be made as a matter of urgency by imaging.

Subacute reversible ataxia may occur as a result of viral infection in children 2-10 years of age. There is usually pyrexia, limb and gait ataxia, and dysarthria developing over hours or days. Recovery occurs over a period of weeks and is usually complete but can take up to 6 months. In older patients the possibility of a post-infectious encephalomyelitis, particularly that related to varicella infection should be considered.

Other causes of subacute ataxia include hydrocephalus, foramen magnum compression, posterior fossa tumour (primary or secondary), abscess, or parasitic infection in any age group. A number of

important toxins and drugs also need to be considered including thallium, lead, barbiturates, phenytoin, piperazine, alcohol, solvents, and anti-neoplastic drugs.

Transient ischaemic attacks involving the vascular supply to the cerebellum rarely produce ataxia and dysarthria alone; usually there are associated symptoms of brain stem dysfunction. Cerebellar infarction (embolus or vertebrobasilar occlusive disease) and haemorrhage (hypertension, vascular malformation or tumour) are relatively rare.

Ataxia with an Episodic Course

- Remember Episodic Ataxia 1 and Episodic Ataxia 2
- In children and young adults a metabolic disorder should be suspected, particularly defects of the urea cycle, aminoacidurias, Leigh's syndrome, and mitochondrial encephalomyopathies. Screening investigations include blood ammonia, pyruvate, lactate and amino acids, and urinary amino acids.

Ataxia with a Chronic Progressive Course

- Chronic alcohol abuse is probably the commonest causes of progressive cerebellar degeneration in adults. Thiamine deficiency is probably the main (but not sole)
- Remember Vitamin E and very rarely Zinc deficiency
- Toxins including drugs e.g. antiepileptic drugs (acute toxicity and chronic use)
- Structural lesions such as posterior fossa tumours, foramen magnum compression, or hydrocephalus must be excluded by imaging studies. Tumours which may involve the posterior fossa include: astrocytoma, ependymoma, haemangioblastoma and cranial nerve neuromas
- Paraneoplastic cerebellar degeneration related to carcinomas of the lung or ovary or to the reticulososes usually follows a subacute course, with patients losing the ability to walk within months of onset. A variety of anti-neuronal antibodies may be found in these patients and help to confirm the diagnosis (see Rees 1999 for review)
- Rarely infectious agents can cause slowly progressive ataxia, these include the chronic panencephalitis of congenital rubella infection in children and, in adults, Creutzfeldt-Jakob disease, particularly the iatrogenic form should be considered
- Superficial siderosis is a rare disorder that causes slowly progressive cerebellar ataxia, mainly of gait, and sensorineural deafness, often combined with spasticity, brisk reflexes, and extensor plantar responses. The diagnosis may not be suspected clinically, but the neuroradiological abnormalities are striking.

After excluding acquired causes of ataxic disorders, there remain a considerable number of patients with degenerative ataxias, not all of which are overtly genetically determined. The inherited ataxias can largely be classified according to their clinical and genetic features (see below), and in a small proportion of cases a recognizable metabolic defect can be detected. It is important to make as accurate diagnosis as possible in these disorders for the purposes of prognosis, genetic counselling, and, occasionally, specific therapy.

Progressive Metabolic Ataxias

- The sphingomyelin lipidoses, metachromatic leukodystrophy, galactosylceramide lipidosis (Krabbe's disease), and the hexosaminidase deficiencies. Also within this group is adrenoleukomyeloneuropathy, a phenotypic variant of adrenoleukodystrophy. This is diagnosed by estimation of very long chain fatty acids. Although X-linked approximately 10% of carrier females may manifest neurological abnormalities
- Cholestanolosis (also called cerebrotendinous xanthomatosis-CTX) is a rare autosomal recessive disorder caused by defective bile salt metabolism, caused by a deficiency of mitochondrial sterol 27 hydroxylase. It gives rise to ataxia, dementia, spasticity, peripheral neuropathy, cataract, and tendon xanthomata in the second decade of life. Treatment with chenodeoxycholic acid appears to improve neurological function

- Various phenotypes that are classifiable as hereditary ataxias have been described in the mitochondrial encephalomyopathies many of which are associated with a defect of mitochondrial DNA including the Kearns-Sayre syndrome.

Acquired Metabolic and Endocrine Disorders Causing Cerebellar Dysfunction

- Hepatic encephalopathy, pontine and extrapontine myelinolysis related to hyponatremia, and hypothyroidism.

Ataxic Disorders Associated with Defective DNA Repair

- Ataxia telangiectasia
- Xeroderma pigmentosum and Cockayne's syndrome.

Hereditary Ataxias

As a useful rule of thumb if one is considering a genetic form of ataxia it is worth noting the age at onset. Onset before the age of 20yrs is most likely to be autosomal recessive. Onset after age 25yrs is most likely autosomal dominant. X linked inheritance is very rare and for some rare complicated forms mtDNA abnormalities may need to be considered.

Autosomal Recessive Ataxias (ARCs)

Friedreich's ataxia (FA) is the most common of the autosomal recessive ataxias and accounts for at least 50% of cases of hereditary ataxia in most large series reported from Europe and the United States. The prevalence of the disease in these regions is similar, between 1 and 2 per 100,000.

The age of onset of symptoms, generally with gait ataxia, is usually between the ages of 8 and 15 years, but onset between 20 and 30, but fulfilling all other diagnostic criteria (Harding 1981), have been described (De Michele et al. 1989). In addition to the progressive ataxia, one finds a number of variable features, including dysarthria, and pyramidal tract involvement. Initially this latter feature may be mild, with just extensor plantar responses, but after five or more years duration of the disease, invariably a pyramidal pattern of weakness in the legs is seen. Eventually this can lead to paralysis. Distal wasting, particularly in the upper limbs, is seen in about 50% of patients with FA. Skeletal abnormalities are also commonly found including scoliosis (85%) and foot deformities typically pes cavus in approximately 50% of patients. Additional clinical support for one's suspicions include optic atrophy which can be seen in 25%, however, it is rare (<5%) for Friedreich's to produce major visual impairment. Deafness is found in less than 10%, but rather more have impairment of speech discrimination (Harding 1984). Nystagmus is seen in only about 20%, but the extraocular movements are nearly always abnormal, with broken-up pursuit, dysmetric saccades, square wave jerks, and failure of fixation suppression of the vestibulo-ocular reflex.

Investigation of patients reveals an axonal sensory neuropathy; an abnormal ECG in 65% of patients with widespread T-wave inversion. (Harding 1984). Diabetes mellitus occurs in 10% of patients with FA, and a further 10-20% have impaired glucose tolerance.

The gene frataxin was cloned in 1996 (Campuzano et al 1996). The predominant mutation is a trinucleotide repeat (GAA) in intron 1 of this gene. Expansion of both alleles is found in over 96% of patients. The remaining patients have point mutations in the frataxin gene. This was the first autosomal recessive condition found to be due to a dynamic repeat and it has permitted the introduction of a specific and sensitive diagnostic test, as it is a relatively simple matter to measure the repeat size. On normal chromosomes the number of GAA repeats varies from 7 to 22 units, whereas on disease chromosomes, the range is anything from around 100 to 2,000 repeats. The length of the repeat is a determinant of age of onset and therefore to some degree influences the severity in that early onset tends to progress more rapidly.

There is accumulating evidence that frataxin is mitochondrially located and may be involved in iron transport. Clinically this fits; a syndrome of ataxia and neuropathy, in association with diabetes,

cardiomyopathy, deafness and optic atrophy, has the hallmarks of a mitochondrial disease. The other ARCAs are very rare and are summarised in Table 2.

Table 2 Autosomal Recessive Ataxias

Syndrome	Gene defect	Clinical notes
Friedreich's ataxia	GAA repeat (and some point mutations in FRDA gene)	Neuropathy, pyramidal signs, skeletal abnormalities, diabetes and cardiomyopathy
Ataxia Telangiectasia AT-like disorder	ATM hMRE11	Oculomotor apraxia, Mixed movement disorder, humoral immune difficulties, increased cancer risk
Cockayne's syndrome	CS-type A- ERCC8 gene CSA- type B- ERCC6 gene	'cachectic dwarfism' Mental retardation Pigmentary retinopathy
Xeroderma pigmentosum	ERCC2 but also probably genetically complex	Skin disorder and an increased risk on skin cancer
AOA1	Aprataxin	Oculomotor apraxia
AOA2	Senataxin	Oculomotor apraxia
Hypogonadism	Not known	Hypogonadotropic hypogonadism
Marinesco-Sjogren syndrome	SIL1 on chr 5q31	Cataracts and mental retardation
Progressive myoclonic ataxia, (Ramsay Hunt syndrome)	Genetically complex	Epilepsy is common
Behr's and related syndromes Eg 3-methylglutaconic aciduria type III (Costeff syndrome)	No gene for Behr's yet identified OPA3 gene	Optic atrophy, spasticity and mental retardation
Congenital or childhood onset deafness	Genetically complex	Syndromic diagnosis –likely to have several causes
Autosomal recessive late-onset ataxia	Heterogeneous	Wide clinical variability

Autosomal Dominant Ataxias

The ADCAs are a clinically and genetically complex group of neurodegenerative disorders. ADCA type I is characterized by a progressive cerebellar ataxia and is variably associated with other extracerebellar neurological features such as ophthalmoplegia, optic atrophy, peripheral neuropathy, pyramidal and extrapyramidal signs. The presence and severity of these signs is, in part, dependent on the duration of the disease (Harding, 1982, 1993). Mild or moderate dementia may occur but it is usually not a prominent early feature. ADCA type II is clinically distinguished from the ADCA type I by the presence of pigmentary macular dystrophy (Enevoldsen *et al* 1994), whereas ADCA type III is a relatively 'pure' cerebellar syndrome and generally starts at a later age. This clinical classification is still useful, despite the tremendous improvements in our understanding of the genetic basis, because it provides a framework which can be used in the clinic and helps direct the genetic evaluation (Table 3).

Table 3 Clinical Impact of the ADCA

ADCA Type	Genetic tests (widely available)	Relative contribution to each subclass
ADCA I	SCA 1, 2, 3	50%
ADCA II	SCA 7	99%
ADCA III	SCA 6	50%

The genetic loci causing the dominant ataxias are given the acronym SCA (spino-cerebellar ataxia). There are currently over 28 SCA loci identified (see Matilla et al 2006 for review). Of these there are genetic tests fairly widely available for SCA's 1, 2, 3, 6, and 7 (see table 3). Interestingly they are all caused by a similar mutational mechanism, an expansion of an exonic CAG repeat. The resultant proteins all possess an expanded polyglutamine tract and there are now at least 8 conditions caused by these expansions. Other types of ADCA are exceedingly rare.

Idiopathic Degenerative Late-Onset Ataxias

About two-thirds of cases of degenerative ataxia developing over the age of 20 years are singleton cases, and they represent a significant clinical problem; it is difficult even to know how to label them. The literature is confusing mixing pathological terms such as olivo-ponto-cerebellar atrophy (OPCA) with clinical terms I prefer to use the term "idiopathic late-onset cerebellar ataxia" (ILOCA). A proportion of patients in this group, progress to develop the features of multiple system atrophy (MSA).

Most patients with idiopathic late-onset cerebellar ataxia lose the ability to walk independently between 5 and 20 years after onset, and life span is slightly shortened by immobility. Those who go on to develop MSA have a particularly poor prognosis.

There is a very recently defined condition which has been added to the differential diagnosis of mid to late life onset progressive ataxias. Carriers of a fragile X syndrome premutation (55-200 CGG repeats) has been reported in patients with a late onset ataxia syndrome with prominent tremor and associated cognitive decline (FXTAS) (Jacquemont et al 2004). Pathological examination has revealed the presences of novel proteinaceous nuclear inclusions in both neurones and astrocytes which are ubiquitin positive but dissimilar to the inclusions of PD, Alzheimer's disease and other tauopathies nor do they resemble the nuclear inclusions seen in CAG repeat disease. Imaging reveals generalised volume loss of cerebrum and cerebellum and signal changes in the middle cerebellar peduncles. Diagnosis is appropriately selected clinical cases is by genetic analysis of the FMR1 repeat.

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