15 Spinocerebellar Ataxias

Professor N Wood

Professor of Clinical Neurology and Neurogenetics, Institute of Neurology, Queen Square, London

Introduction

The term ataxia derived from the Greek means "irregularity" or "disorderliness." Unsteadiness can result from a number of causes, including poor vision, impairment of postural reflexes, or due to a deficiency of sensory input, i.e. sensory ataxia. This chapter 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. It should, however, be noted that clinical assessment is complicated by the fact that many ataxic patients have additional pathology in the brain stem, spinal cord, or elsewhere.

Symptoms of Ataxic Disorders

The history is extremely important and the commonest presenting complaints are of gait unsteadiness or slurring of speech. Some refer to "giddiness" or "dizziness" when they really mean unsteadiness of gait without associated vertigo or light headedness. The two single most important features to take note of are age at onset and rate/pattern of disease. Finally, because of huge progress in genetics a detailed family history is paramount.

Disturbances of Gait

This is the most frequent presenting feature in ataxic disorders. A particular note of age at onset and rate of progression, highlighted with questions about early motor milestones, sporting ability compared to peers at school.

Limb Incoordination and Tremor

Clumsiness of the arms is often noted as their illness progresses. Generally a tremor that is worse on action is reported and as this worsens patients notice clumsiness carrying objects and deterioration of their handwriting. Titubation is typically seen in midline cerebellar lesions.

Dysarthria

This may be noted by friends and relatives before the patient. Classically described as having a staccato quality and is a useful symptom or sign as it points against a purely sensory ataxia. It is also worth listening to the speech as many patients have a dysarthria with cerebellar features mixed with spastic or dysphonic elements.

Visual and Oculomotor Symptoms

Visual symptoms are relatively rare in pure cerebellar disease and if present is more often associated with brain stem disturbance, especially episodic or persistent diplopia associated with ataxia. Vertical oscillopsia suggests downbeat nystagmus and a structural foramen magnum lesion should be suspected. Acute or subacute oscillopsia, with chaotic involuntary eye movements, may be mentioned in the history of patients with viral cerebellitis, paraneoplastic cerebellar degeneration, and the dancing-eyes syndrome (opsoclonus).

Other Symptoms

Direct questioning should cover the urinary system, skeletal deformities, cardiac disease, and assessment of cognitive abilities, since many ataxias can be associated with disease in other systems (Table 1).

A detailed inquiry of drug ingestion (for both medical and recreational purposes, including alcohol) and occupational exposure is also required.

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	Argininosuccinicaciduria	Brittle
	Giant axonal neuropathy	Tight curls
	Thallium poisoning, hypothyroidism, adrenoleukomyeloneuropathy	Loss
	Foramen magnum lesions	Low hairline
Skin	Ataxia telangiectasia	Telangiectases, particularly conjunctiva, nose, ears, flexures
	Xeroderma pigmentosum	Extreme light sensitivity, tumours
	Hartnup disease	Pellagra-type rash
	Cholestanolosis	Tendinous swellings
	Hypothyroidism, Refsum's disease, Cockayne syndrome	Dry skin
	Adrenoleukomyeloneuropathy	Pigmentation
Eyes	Ataxia telangiectasia	(see Skin)
	Wilson's disease	Kayser-Fleischer rings
	Cerebellar hemangioblastoma	Retinal angiomas in von-Hippel-Lindau disease
	Congenital rubella, cholestanolosis, Sjögren-Larsson syndrome	Cataract
	Gillespie syndrome	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	Cardiomegaly,murmurs, arrhythmias, late heart failure, abnormal ECG
	Mitochondrial encephalomyopathy	Conduction defects

Signs of Cerebellar Disease

It is generally good practice in neurology to greet the patient in the waiting room; observe them rising from a chair mobilising to the consulting room, shaking hands and hearing their speech. In the case of the ataxic patient this sequence provides much of the information one needs to characterise the disease.

Gait and Posture

A patient walking into the consulting room may have a broad-based gait, with a poor turn. More detailed assessment of mild gait ataxia may be obtained by asking the patient to tandem walk (heel-toe). Asking the patient to stand still may reveal the broad base and also permits the assessment of proprioception via Romberg's test.

Speech

It is often stated that cerebellar speech is very distinctive with an explosive quality, so-called scanning dysarthria. Although when this is heard it is characteristic. Often a combination of cerebellar and

spastic features may be heard. Additional signs such as a slow moving tongue and brisk jaw jerk support the latter.

Limb Ataxia

Limb ataxia is usually assessed by looking for evidence of dysmetria and dysdiadochokinesis. Dysmetria is most simply assessed using finger nose and heel shin tests. Dysdiadochokinesis is demonstrated by asking the patient to tap one hand on the other, alternately pronating and supinating the tapping hand, or rapidly opening and closing the fist. In addition the tapping out of simple rhythms (with the hand or foot) is also useful for assessing both the rhythmicity and force of the tap.

It is worth noting that the dominant limb will be naturally a bit better than the non-dominant limb, so beware over-calling asymmetry. About 40% of patients with vermis lesions do not have limb ataxia but have prominent 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. Titubation with a frequency of 3-4 Hz may be seen with midline cerebellar disease.

Eye Movements

This is perhaps the most sensitive of the assessments to evaluate the patient with suspected cerebellar disease. It is important to search for:

- Square wave jerks in the primary position
- Jerkiness of pursuit, also variously called saccadic pursuit, saccadic intrusions into pursuit
- Detailed assessment of saccades, including initiation, velocity, dysmetria, accuracy
- An assessment of Dolls Head Manoeuvre and its suppression can provide further clarity.

Gaze-evoked nystagmus is the most common type of nystagmus associated with cerebellar disease: eccentric gaze cannot be maintained and the slow phase of the nystagmus is toward the primary position, with rapid corrective movements. Apart from down beat nystagmus which may indicate a foramen magnum lesion, gaze evoked nystagmus is of limited localisation value in most forms of ataxia.

Positional nystagmus in a patient with vertigo and unsteadiness should be attributed to benign labyrinthine disease only if it is transient, torsional, and fatigable; if it does not have these features, a posterior fossa lesion should be suspected.

Other Neurological Signs and General Examination

As the causes of ataxia are numerous, a large variety of other neurological and general physical signs may be found on examination. The range of these and their possible diagnostic significance is shown in Table 1.

Investigations

This is necessarily a brief overview of a complex area.

Imaging

Clearly, imaging has had a massive impact on clinical neuroscience. For the ataxias, it helps identify structural lesions (e.g. tumours, vascular events, and demyelination). It may also confirm the clinical impression of a degenerative process with the presence of atrophy. The current limitations of MRI for monitoring disease progression are still limited and generally not that clinically useful as there is a poor correlation between severity of symptoms and degree of atrophy.

Genetics

There are some gene tests that are widely available (e.g. FRDA and some of the SCAs). Several diagnostic laboratories are now offering a broader range of tests on so called gene panels and this will be rapidly followed by the clinical application of whole exome and whole genome sequencing approaches. This will provide much greater clarity as to potential genetic causes underlying the congenital and genetic syndromes.

Quantifying the Anatomy

Many of the conditions discussed in this chapter are complex and this author has a low threshold for requesting further investigations to help identify and quantify other deficits. This includes nerve conduction studies (e.g. the presence of a demyelinating neuropathy rather than axonal can help in dissecting the differential diagnosis; a sensory neuropathy points to a different group of disorders compared to a generalised neuropathy).

Disorders of the Cerebellum

Developmental Disorders

The cerebellum has a long developmental period and is not fully mature until about 18 months of age. It is therefore susceptible to a large number of insults, including intrauterine infections, ischaemic damage, toxins and genetically determined syndromes (Table 2). These are generally non-progressive disorders and in most cases coordination improves somewhat with age. Increasingly genetic abnormalities are being discovered to account for some of these disorders.

Table 2 Congenital inherited ataxic disorders

Syndrome	***Genetics***	***Additional features***
Joubert's syndrome	Autosomal recessive AHI1 gene NPHP1 gene CEP290 Plus others with established and distinct loci	With episodic hyperpnoea, abnormal eye movements, and mental retardation
Gillespie's syndrome	Uncertain inheritance No gene or locus known	With mental retardation and partial aniridia
Congenital ataxia with mental retardation and spasticity	autosomal recessive, autosomal dominant, and X-linked NYS1 -6p NYS2- X linked And others	Includes pontoneocerebellar and granule cell hypoplasia
Disequilibrium syndrome	autosomal recessive	
Paine's syndrome	X-linked recessive ataxia- no gene identified	With spasticity, mental retardation and microcephaly

Ataxia of Acute or Subacute Onset

As with other aspects of neurology, acute onset equals a vascular process until proven otherwise. Sub-acute raises the possibility of infectious, para-infectious, or immune (including paraneoplastic) disorders.

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 antineoplastic drugs.

Ataxia with an Episodic Course

These attacks may be considered bizarre and some patients are misdiagnosed as non-organic. However, a good history can usually distinguish between the main causes (in order of approximate frequency): drug ingestion, multiple sclerosis, transient vertebrobasilar ischaemic attacks, foramen

magnum compression, intermittent obstruction of the ventricular system due to a colloid cyst or cysticercosis, and a growing list of inherited episodic ataxias (see Baloh 2012 and Russell et al 2103 for reviews)

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 serum 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 the main (but not sole) explanation for the chronic progressive cerebellar syndrome found in alcoholics. Patients with this syndrome are frequently malnourished timely treatment with thiamine is essential.

There are other deficiency disorders that can give rise to a progressive ataxia. There is a rare syndrome associated with zinc deficiency that responds to oral replacement therapy. Deficiency of vitamin E, either genetic (e.g. isolated vitamin E deficiency due to mutations in α-tocopherol transfer protein (Gotoda et al 1995, or abetalipoproteinaemia) may produce a progressive ataxia. Establishing the diagnosis of vitamin E deficiency is important as treatment with vitamin E may prevent progression of the neurological syndrome and can in rare circumstances lead to some improvement.

Toxic exposures should be considered and include pharmaceutical products (e.g. phenytoin and other AEDs), solvents (e.g. toluene), and heavy metals (e.g. inorganic mercury, lead and thallium).

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 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 (reviewed by Vernino 2012). Presentation with ataxia precedes diagnosis of the malignancy in 70% of cases and is usually subacute, progressing to severe disability over several months or even weeks and then arresting. There is currently no proof that immunosuppressant therapy, or plasma exchange improves outlook for immune-mediated cerebellar disease.

Rarely infectious agents can cause slowly progressive ataxia (Table 3) These include the chronic panencephalitis of congenital rubella infection in children and, in adults, Creutzfeldt-Jakob disease, particularly the iatrogenic form should be considered. A specific enquiry regarding potential risk factor exposure should be sought, especially growth hormone replacement although, following introduction of stringent controls on source material, this has become extremely rare. Multiple sclerosis only exceptionally presents as an isolated chronic progressive cerebellar syndrome.

Table 3 Infections causing cerebellar disease

Viruses	***Others***
Echo	Mycoplasma pneumoniae
Coxsackie groups A and B	Legionella pneumoniae
Herpes simplex	Lyme disease
Poliovirus	Toxoplasma gondii
Epstein-Barr	typhoid fever
Varicella	Plasmodium falciparum
Congenital rubella	Tick paralysis
	Prion disease

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: MRI showing a black rim of haemosiderin around the posterior fossa structures and spinal

cord, and less often the cerebral hemispheres, on T2-weighted images. Superficial siderosis is most commonly secondary to chronic leaking of blood into the subarachnoid space (see Fearnley et al 1995 and Charimidiou 2015 for reviews).

Progressive Metabolic Ataxias

Ataxia may be a minor feature of storage and other metabolic neurodegenerative disorders developing in early childhood. Some enzyme deficiencies that usually give rise to diffuse neurodegenerative disorders, in which ataxia is a feature, developing in infancy or early childhood, include 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.

Acquired Metabolic and Endocrine Disorders Causing Cerebellar Dysfunction

Acquired metabolic and endocrine disorders causing cerebellar dysfunction include hepatic encephalopathy, pontine and extrapontine myelinolysis related to hyponatremia, and hypothyroidism. The latter is only very rarely a cause of a cerebellar syndrome in both children and adults.

Degenerative Disorders

The degenerative cerebellar and spinocerebellar disorders are a complex group of diseases, most of which are genetically determined. In some there is an underlying metabolic disorder, and it is important to diagnose these, as there may be important implications for treatment and genetic counselling. There has been a rapid growth in our knowledge of the genetic basis of many of the spinocerebellar degenerations. The current phase of research is focussed on how these genes and the abnormal proteins they produce cause cell specific neuropathology. Inherited ataxic disorders can be divided according to their mode of inheritance (Tables 4 and 5). Most autosomal recessive disorders are of early onset (less than 20 years), and autosomal dominant disorders are usually of later onset (over 20 years). For a recent review of genetics of ataxia see Storey 2014. For prevalence estimates see Ruano et al 2014.

Autosomal Recessive Ataxias

Friedreich's Ataxia

This is the most common of the autosomal recessive ataxias (see Table 4) 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 later onset cases are well recognised. In essence it produces a complicated ataxia with pyramidal and axonal neuropathic pathologies. Skeletal abnormalities are also commonly found including scoliosis (85%) and foot deformities typically pes cavus in approximately 50% of patients. One can also find optic atrophy, sensori-neural hearing loss, cardiomyopathy and diabetes (Harding 1981).

It was perhaps not a surprise that the protein encoded by the frataxin gene has subsequently been shown to be a nuclear encoded mitochondrial protein and appears to be involved in iron transport. Recent work has suggested that epigenetic approaches may prove useful in treating this disease (Sandi et al 2014)

The gene frataxin was identified 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 one expansion and a point mutation 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.

Table 4: Autosomal recessive ataxias (onset usually before 20 years of age)

Syndrome	*Gene defect*	*Clinical notes*
Friedreich's ataxia	GAA repeat (and rarely point mutations in FRDA gene)	Neuropathy, pyramidal signs, skeletal abnormalities, diabetes and cardiomyopathy
ARSACs	Sacsin	Demyelinating neuropathy and hypertrophied retinal nerve fibre layer (on OCT)
Ataxia Telangiectasia AT-like disorder	ATM hMRE11	Oculomotor apraxia, Mixed movement disorder, humoral immune difficulties, increased cancer risk
Cockaynes 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
Progressive myoclonic ataxia, (Ramsay Hunt syndrome)	Genetically complex	Epilepsy is common
Congenital or childhood onset deafness	Genetically complex	Syndromic diagnosis –likely to have several causes

Other Recessive Ataxias

These are individually rare but increasingly, with widespread adoption of whole exome and whole genome sequencing strategies, they are being genetically clarified.

Ataxic Disorders Associated with Defective DNA Repair

There are several rare disorders which are characterized at a molecular level by a reduced capacity to repair DNA. The most well known is ataxia telangiectasia (AT). Characteristically, motor development is often delayed and ataxia noted at the time of first walking. Growth retardation and delayed sexual development are frequent, and there is mild mental retardation in some cases (Woods and Taylor 1992). A mixed movement disorder may be seen, often with a combination of ataxia, dystonia, and chorea. The cutaneous telangiectasia of AT tend to develop on the conjunctivae between the ages of 3 and 6 years, but occasionally are inconspicuous or absent in adult life. AT is associated with abnormalities of both humoral and cell-mediated immunity. Genetics and clinical features have recently been reviewed by Tieve et al 2015.

Ataxia Associated with Oculomotor Apraxia.

There are 2 genetically distinct but clinically similar disorders associated with the distinctive feature of oculomotor apraxia- types 1 and 2. Oculomotor apraxia represents a deficit of the voluntary saccadic system and should be suspected in the presence of head thrusts or synkinetic blinking which are used to help initiate a voluntary saccade. AOA1, is dues to mutations in aprataxin and AOA2 is dus to abnormalities in senataxin. This latter condition along with ARSACs represent the second most common casue sof ARCA after FRDA. Testing for ATM, aprataxin and senataxin is now possible in specialised labs

The finding of mutations in a gene called sacsin as the cause of a complicated form of autosomal recessive ataxia (Autosomal recessive ataxia of Charlevoix Sagueney- ARSCAS) proved illuminating. Hitherto it had been appreciated as an extremely rare form originating in small community in Quebec. A very recent review by Pilliod et al (2015) provides useful insights into clinical features and diagnostic criteria.

Autosomal Dominant Ataxias

The ADCAs are a clinically and genetically complex group of neurodegenerative disorders (see Table 5a and 5b). 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. ADCA type II is clinically distinguished from the ADCA type I by the presence of pigmentary macular dystrophy, whereas ADCA type III is a relatively 'pure' cerebellar syndrome and generally starts at a later age. This clinical classification is still useful, despite improvements in our understanding of the genetic basis (see below), because it provides a framework which can be used in the clinic and helps direct the genetic evaluation.

Loci causing dominant ataxias are given the acronym SCA (spino-cerebellar ataxia). There are over 36 SCA loci identified (Sailer et al 2012). With discovery of the genes it became apparent that some of these are duplicates and yet there are still more to be found. In general clinical practice 5 of these the genes are established (SCA's 1, 2, 3, 6, and 7). They are all caused by a similar mutational mechanism: 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 (see HD chapter and Everett and Wood 2004). Other ADCAs are rare and mutation testing is only available for a small number.

Table 5a Autosomal dominant cerebellar ataxia: clinico-genetic classification (onset usually over age of 25 years). List of currently identified genes divided by ADCA subtype to facilitate clinical relevance.

ADCA Type	***Clinical Features***	***Genetic Loci and Chromos***	***Gene***
ADCA I	Cerebellar syndrome plus: Pyramidal signs Supranuclear ophthalmoplegia Extrapyramidal signs Peripheral neuropathy Dementia	SCA 1	Ataxin 1 CAG
		SCA 2	Ataxin 2 CAG
		SCA 3	Ataxin 3 CAG
		SCA 8	Kelch-like 1 CTG repeat
		SCA12	PPP2R2B CAG repeat
		SCA13	KCNC3 Point mutations
		SCA14	PRKCG Point mutations
		SCA 15	ITPR1
		SCA 17	TBP CAG
ADCA II	Cerebellar syndrome plus: Pigmentary maculopathy Other signs as ADCA I	SCA 7 3p12-21.1	Ataxin 7 CAG
ADCA III	"Pure" cerebellar syndrome Mild pyramidal signs	SCA 5	SPTBN2 Beta-III spectrin D,
		SCA 6	CACNL 1A # CAG repeat
		SCA 10	Ataxin 10 ATTCT repeat
		SCA 11	TTBK2
		SCA 27	FGF14 Point mutations
Episodic ataxias	EA 1		Kv1.1
	EA 2		CACNL 1A #

SCA6 and CACNL1A are allelic variants.

Table 5b 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%

Idiopathic Degenerative Late-Onset Ataxias

About two-thirds of cases of degenerative ataxia developing over the age of 20 years are isolated 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). These patients may have or develop facial impassivity and extrapyramidal rigidity whilst others present with features of autonomic failure such as postural hypotension, impotence, bladder dysfunction, and a fixed cardiac rate. A cerebellar presentation occurs in about 30% of patients with MSA (see Gilman et al 2008 for consensus criteria). The distinction of idiopathic late-onset cerebellar ataxia from MSA may therefore be difficult clinically at presentation.

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.

The role of gliadin sensitivity in producing a chronic progressive ataxia (and indeed other neurological conditions, either as part of Coeliac disease or as a purely neurological phenotype is still debated (Hadjivassiliou et al 2003,). A recent meta-analysis in children did not identify a significant risk above the general population (Lionetti et al 2010)

Over the last decade a newly recognised condition has been shown to explain a small minority of cases. Usually male patients in mid to late life develop a progressive phenotype of ataxia and tremor in association with an intermediate expansion in the fragile X gene. This has been termed FXTAS (Fragile X Tremor Ataxia Syndrome) (Jacquemont et al 2004). A recent review by Hagerman and Hagerman (2015) provides useful details of the core features and variable phenoptypes associated with this mutation.

References

Baloh RW. Episodic ataxias 1 and 2. Handb Clin Neurol. 2012;103:595-602. doi: 10.1016/B978-0-444-51892-7.00042-5.

Campuzano V, Montermini L, Molto MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* 1996;271:1423-1427.

Everett CM, Wood NW. Trinucleotide repeats and neurodegenerative disease. Brain. 2004;127:2385-405.

Fearnley JM, Stevens JM, Rudge P. Superficial siderosis of the central nervous system. Brain 1995;118:1051-66

Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Dürr A, Fowler CJ, Kaufmann H, Klockgether T, Lees A, Poewe W, Quinn N, Revesz T, Robertson D, Sandroni P, Seppi K, Vidailhet M. Second consensus statement on the diagnosis of multiple system atrophy.Neurology. 2008;71:670-6.

Gotoda T Arita M, Arai H, Inoue K, Yokota T, Fukuo Y, Yazaki Y, Yamada N. Adult-onset spinocerebellar dysfunction caused by a mutation in the gene for the □-tocopherol transfer protein. N Engl J Med 1995;333:1313-1318.

Hadjivassiliou M, Grunewald R, Sharrack B, Sanders D, Lobo A, Williamson C, Woodroofe N, Wood N, Davies-Jones A. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. Brain. 2003;126:685-91

Hagerman PJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome.
Ann N Y Acad Sci. 2015 Mar;1338:58-70. doi: 10.1111/nyas.12693. Epub 2015 Jan 26.

Hanna MG, Wood NW, Kullmann D. The Neurological Channelopathies. J Neurol Neurosurg Psych 1998;65:427-431.

Harding AE. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. Brain 1981; 104:589-620.

Jacquemont S, Hagerman RJ, Leehey MA, Hall DA, Levine RA, Brunberg JA, Zhang L, Jardini T, Gane LW, Harris SW, Herman K, Grigsby J, Greco CM, Berry-Kravis E, Tassone F, Hagerman PJ. Penetrance of the fragile X-associated tremor/ataxia syndrome in a premutation carrier population. JAMA. 2004;291:460-9.

Lionetti E, Francavilla R, Pavone P, Pavone L, Francavilla T, Pulvirenti A, Giugno R, Ruggieri M. The neurology of coeliac disease in childhood: what is the evidence? A systematic review and meta-analysis. Dev Med Child Neurol. 2010 Aug;52(8):700-7. doi: 10.1111/j.1469-8749.2010.03647.

Moreira MC, Klur S, Watanabe M, Nemeth AH, Le Ber I, Moniz JC, Tranchant C, Aubourg P, Tazir M, Schols L, Pandolfo M, Schulz JB, Pouget J, Calvas P, Shizuka-Ikeda M, Shoji M, Tanaka M, Izatt L, Shaw CE, M'Zahem A, Dunne E, Bomont P, Benhassine T, Bouslam N, Stevanin G, Brice A, Guimaraes J, Mendonca P, Barbot C, Coutinho P, Sequeiros J, Durr A, Warter JM, Koenig M. Senataxin, the ortholog of a yeast RNA helicase, is mutant in ataxia-ocular apraxia 2. Nat Genet. 2004;36:225-7.

Pilliod J, Moutton S, Lavie J, Maurat E, Hubert C, Bellance N, Anheim M, Forlani S, Mochel F, N'Guyen K, Thauvin-Robinet C, Verny C, Milea D, Lesca G, Koenig M, Rodriguez D, Houcinat N2, Van-Gils J, Durand CM, Guichet A, Barth M, Bonneau D, Convers P, Maillart E, Guyant-Marechal L21, Hannequin D, Fromager G, Afenjar A, Chantot-Bastaraud S, Valence S, Charles P, Berquin P, Rooryck C, Bouron J, Brice A, Lacombe D, Rossignol R, Stevanin G, Benard G, Burglen L, Durr A, Goizet C, Coupry I. New practical definitions for the diagnosis of autosomal recessive spastic ataxia of Charlevoix-Saguenay Ann Neurol. 2015 Dec;78(6):871-86. doi: 10.1002/ana.24509. Epub 2015 Nov 14.

Russell JF, Fu YH, Ptáček LJ. Episodic neurologic disorders: syndromes, genes, and mechanisms. Annu Rev Neurosci. 2013 Jul 8;36:25-50. doi: 10.1146/annurev-neuro-062012-170300. Epub 2013 Apr 29.

Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. Neuroepidemiology. 2014;42(3):174-83. doi: 10.1159/000358801.

Ryan MM, Engle EC. Acute ataxia in childhood. J Child Neurol. 2003;18:309-16.

Sailer A1, Houlden H.Recent advances in the genetics of cerebellar ataxias. Curr Neurol Neurosci Rep. 2012 Jun;12(3):227-36. doi: 10.1007/s11910-012-0267-6.

Storey E. Genetic cerebellar ataxias. Semin Neurol. 2014 Jul;34(3):280-92. doi: 10.1055/s-0034-1386766. Epub 2014 Sep 5.

Vernino S Paraneoplastic cerebellar degeneration. Handb Clin Neurol. 2012;103:215-23. doi: 10.1016/B978-0-444-51892-7.00013-9.

Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, Aiba I, Abe Y, Tamakoshi A, Doyu M, Hirayama M, Sobue G. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain. 2002;125:1070-83.