A practical approach to late-onset cerebellar ataxia:

putting the disorder with lack of order into order

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Abstract
The clinical management of cerebellar ataxia is challenging, mainly because ataxia is a symptom of many neurological diseases. Many types of ataxia disorders are genetic and some are extremely rare. Here, the authors suggest a diagnostic approach to ataxia developed around a case of sporadic, late-onset, slowly progressive ataxia. Clinical information such as age of onset, rate of progression, family history and certain non-cerebellar features can narrow the differential diagnosis. Brain MRI is almost obligatory and may reveal valuable diagnostic clues. Having ruled out structural lesions, the two other most common diagnoses are inflammatory and degenerative (including genetic) disorders. Although only a minority of underlying diseases are treatable, there are still many options for supportive care.

Introduction

The clinical management of cerebellar ataxia is challenging for several reasons. First, there is an extensive differential diagnosis, with each condition requiring different investigations. Second, with the study of genetic ataxias progressing rapidly, neurologists cannot easily keep themselves sufficiently updated to select which genes, if any, to test. Third, even 'common' causes of cerebellar ataxia are quite uncommon, making it difficult to build expertise in these disorders. Last, although most cerebellar ataxias are untreatable, clinicians are wrong to assume that they can do little for the patient's well-being. Based on a case history, we suggest a guide to clinical decision-making for patients with ataxia, focusing mainly on sporadic, late-onset (after the age of 30 years) cerebellar ataxia.

Case

A 62-year-old previously well man presented with a 3-year history of gradually worsening unsteadiness and shaking of his hands on action. His speech and swallowing were normal, but there was some urinary urgency. There was no family history. He drank 3–4 glasses of wine a day. On examination, there was titubation, a bilateral terminal tremor on finger–nose testing, dysmetria during finger-chasing, abnormal heel-to-shin testing, mild gait ataxia and clearly disturbed tandem gait, and brisk tendon reflexes with bilateral extensor plantar responses. Investigations showed normal serum vitamin levels and thyroid function; an MR scan of the brain showed cerebellar atrophy, mainly of the vermis.

History and examination: things you get for free

An old-fashioned comprehensive clinical evaluation is important. The causes of cerebellar ataxia are grouped into genetic, acquired and non-genetic neurodegenerative disorders (table 1). A careful history and physical examination allows the clinician to rank these causes in order of suspicion, sometimes with quite a narrow differential. The four important points in the history are: speed of onset/progression, age at onset, family history and some aspects in the general medical history.

Speed of onset/progression

Ataxia presenting abruptly obviously suggests a stroke. Ataxia developing over hours might suggest Wernicke's encephalopathy, although other features are common. Onset over days might suggest Miller Fisher syndrome or para-infectious cerebellitis,

Table 1 Overview of the genetic and non-genetic causes of cerebellar ataxia, with clinical clues from history or examination, and suggestions for initial investigations

Cause	Clinical clues	Suggestions for investigation
Genetic ataxias		
Dominant		
Autosomal dominant cerebellar ataxias	Family history, slowly progressive ataxia, some genotype-specific features (online supplementary table S1)	Mutation analysis of SCA genes
Dentato-rubro-pallidoluysian atrophy	Dementia, chorea, myoclonus, mainly in the Japanese	Mutation analysis of ATN1 gene
Alexander disease	(Pseudo)bulbar signs, spasticity, hyperreflexia	Mutation analysis of GFAP gene
Recessive		
Autosomal recessive cerebellar ataxias	Family history, systemic features, often neuropathy (see also online supplementary table S2)	Mutation analysis of relevant recessive genes, lysosomal enzymes, α-fetoprotein, metabolic investigation
Other		
'Mitochondrial' disorders	Family history (diabetes mellitus, deafness), multisystem involvement	Mutation analysis of polymerase γ and mitochondrial DNA Muscle biopsy
Fragile X-associated tremor/ataxia syndrome	Action tremor, behavioural changes, autonomic dysfunction; family history (learning disability)	Mutation analysis of FMR1 gene, typical MRI (figure 4)
Non-genetic ataxias		
Degenerative		
Multiple system atrophy	Autonomic failure, Parkinsonism	MRI (figure 8), nuclear imaging, autonomic testing, see also online supplementary table S1
Idiopathic late onset cerebellar ataxia	Mostly pure, slowly progressive ataxia	No specific test, other causes excluded
Sporadic Creutzfeldt–Jakob disease	Rapid progression, myoclonus, cognitive disturbances	EEG, CSF 14-3-3 protein/tau, typical MRI (figure 9)
Inflammatory		
Gluten ataxia	Gastro-intestinal symptoms	Antigliadin/-tissue transglutaminase/-endomysium antibodies
Hashimoto encephalopathy	Subacute, seizures, myoclonus	Anti-TPO antibodies
Paraneoplastic cerebellar degeneration	Rapid progression, history of malignancy	Neuronal antibodies, tumour screen
Anti-GAD ataxia	Subacute, type 1 diabetes mellitus	Anti-GAD antibodies
(Para)infectious		
Miller Fisher syndrome	Subacute, ophthalmoplegia, areflexia	Anti-GQ1b antibodies, EMG
Epstein–Barr virus	Subacute, preceding infection	CSF, serologic testing
HIV	Known HIV status	CSF, search for opportunistic infections
Structural lesions		
Stroke, tumour, multiple sclerosis, etc	Focal neurological signs	MRI, other investigations depend on imaging findings
Toxic		
Alcohol	Medical history, peripheral neuropathy	Liver function
Drugs (eg, lithium, phenytoin)	Medical history	Screening drug level, stop offending drug
Metabolic		
Acquired vitamin deficiencies		
Vitamin E	Diarrhoea	Vitamin E level, coeliac screen, serum amylase
Vitamin B_1	Confusion, nystagmus, ophthalmoplegia	Vitamin B_1, typical MRI
Hypothyroidism	Fatigue, weight gain, constipation	Thyroid stimulating hormone, free T4
Hypoparathyroidism	Cataract, extrapyramidal symptoms	Parathyroid hormone, calcium, phosphate, typical CT scan (figure 2)
Other		
Superficial siderosis	Sensorineural deafness	Typical MRI (figure 7), audiogram, xanthochromic CSF

CSF, cerebrospinal fluid; EMG, electromyogram; GAD, glutamic acid decarboxylase; SCA, spinocerebellar ataxia; TPO, thyroperoxidase.

particularly in children. Subacute onset and progression (weeks to months) suggest only a few conditions: paraneoplastic cerebellar degeneration, Creutzfeldt–Jakob disease, steroid-responsive encephalopathy with antithyroid antibodies (SREAT; previously referred to as Hashimoto's encephalopathy) and antiglutamic acid decarboxylase (anti-GAD)-associated cerebellar ataxia.

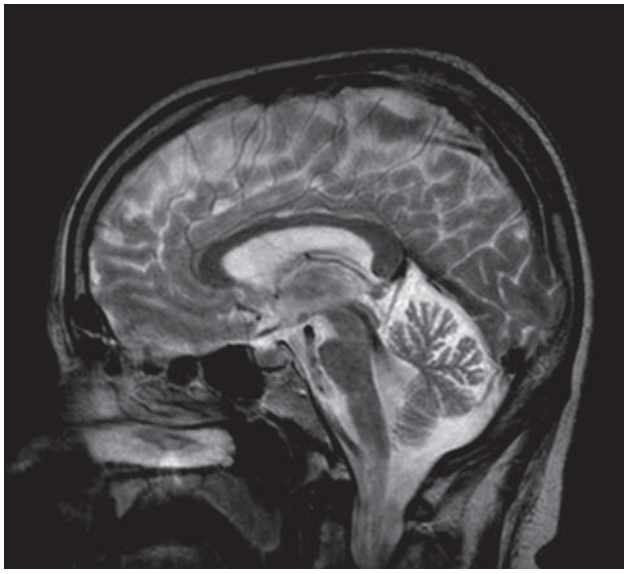

Figure 1 Spinocerebellar ataxia type 2. Cerebellar and pontine atrophy on a sagittal T2-weighted MRI.

Insidious onset with progression over years does not suggest any particular diagnosis but mostly rules out the above-mentioned diseases.

Age at onset

Age at onset is very important. For example, a slowly progressive ataxia starting before the age of 25 years may well be genetic or metabolic. Some disorders rarely appear before a certain age, for example, multiple system atrophy (MSA) always manifests after the age of 30 years and the fragile X tremor/ataxia syndrome (FXTAS) also develops after the age of 45 years.

Family history

A family history of cerebellar ataxia clearly suggests a genetic cause. It is worth investing time in drawing up a full pedigree, as the mode of inheritance determines which mutations to request for investigation. The absence of a family history does not rule out a genetic cause. This is particularly true for recessive disease, as smaller families often have no affected siblings. Consanguinity strongly suggests recessive disease and clinicians should ask for information about this. When going through the family history for ataxia, check also for other movement disorders: for example, spinocerebellar ataxia type 3 (SCA-3) can present with Parkinsonism rather than ataxia, mitochondrial disorders may present with diabetes mellitus and deafness, and FXTAS may present with learning disability and premature ovarian failure.

General medical conditions

A detailed medical history is important since diagnostic clues are possible in any domain. Weight loss may suggest an underlying tumour, weight gain can suggest hypothyroidism, diarrhoea can point to coeliac disease, postural dizziness may indicate MSA and previous—even mild—head trauma may suggest superficial siderosis. A recent malignancy history clearly suggests pareneoplastic cerebellar degeneration. Patients with HIV or AIDS may develop ataxias from opportunistic infections, cerebellar lymphoma or cerebellar degeneration.[1] Check and recheck the alcohol intake and ask for past and present medication.

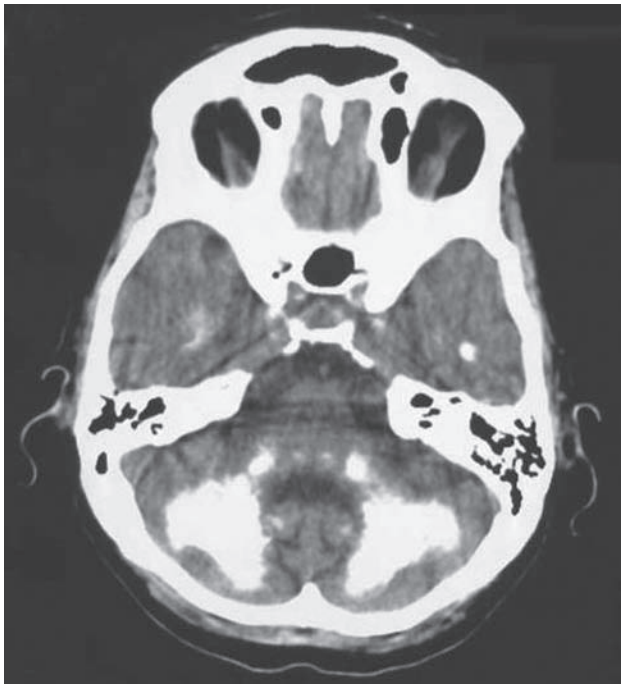

Figure 2 Hypoparathyroidism. Cerebellar calcification on CT brain scan.

Examination

The clinical examination confirms that the ataxia is indeed cerebellar. However, its added value is to identify other relevant neurological and non-neurological features.

- Valuable non-neurological abnormalities include telangiectasias, **scoliosis** and **orthostatic hypotension**.
- A severe **saccadic eye movement disorder** (oculomotor apraxia) immediately points to a very limited number of conditions, such as ataxia telangiectasia and ataxia with oculomotor apraxia type 2.
- Ataxia with **chorea** requires substantially different investigation from ataxia with spasticity; if there is concomitant chorea one should for example consider ataxia telangiectasia or SCA-17, while spasticity combined with ataxia fits with diagnoses such as autosomal recessive spastic ataxia of Charlevoix–Saguenay or late onset Friedreich's ataxia.

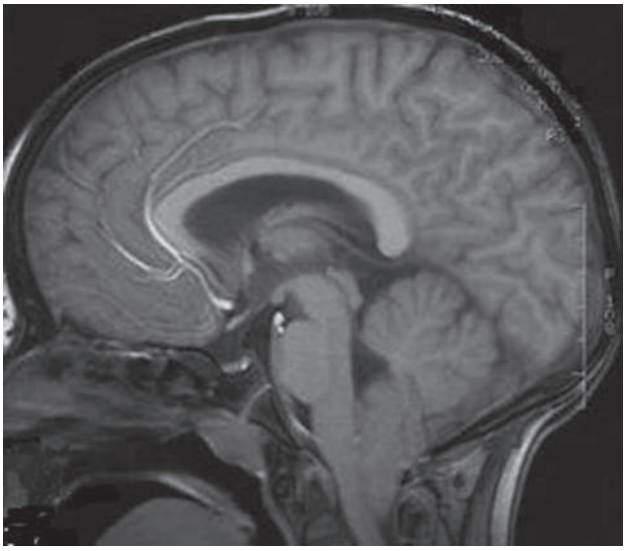

Figure 3 Chiari malformation. Low-hanging, elongated cerebellar tonsils displaced below the level of the foramen magnum on a sagittal T1-weighted MRI.

- The presence or absence of **peripheral neuropathy** (later corroborated by nerve conduction studies) is important in early onset cases (see online supplementary table S3).

Always do a brain MRI

The investigation of patients with cerebellar ataxia should always include—in fact begin with—an MRI brain scan. The only exception might be the patient whose family has a known genetic defect. The MRI first allows demonstration or exclusion of a structural lesion, such as cerebellar tumour or abscess. If there is no such lesion, one should meticulously search the images for other specific abnormalities (see figures).

- **Cerebellar atrophy** usually indicates a degenerative disease (which could be genetic) or to later stages of paraneoplastic cerebellar degeneration (figure 1).
- **Tadpole sign** in adult-onset Alexander disease has very pronounced atrophy of the medulla and cervical cord; with the preserved pons, the sagittal image looks like a tadpole (figure 5).
- **Chiari type I malformation** can lead to cerebellar symptoms, cranial neuropathies and headache, usually in adolescence or adulthood (figure 3).[2]
- **Cerebellar white matter high-signal changes** could indicate polymerase γ (POLG) mutations, Langerhans cell histiocytosis or cerebrotendinous xanthomatosis. FXTAS often gives changes in the middle cerebellar peduncles (figures 6 and 4, respectively).
- **The 'hot cross bun' sign** in the pons occurs in MSA from pontocerebellar fibre degeneration; **a 'putaminal rim'** results from a high signal line extending laterally from a slightly darkened putamen (figure 8).
- **Creutzfeldt–Jakob disease** may give thalamic changes (pulvinar sign) or abnormal cerebral cortex on diffusion-weighted MRI (figure 9).[3]

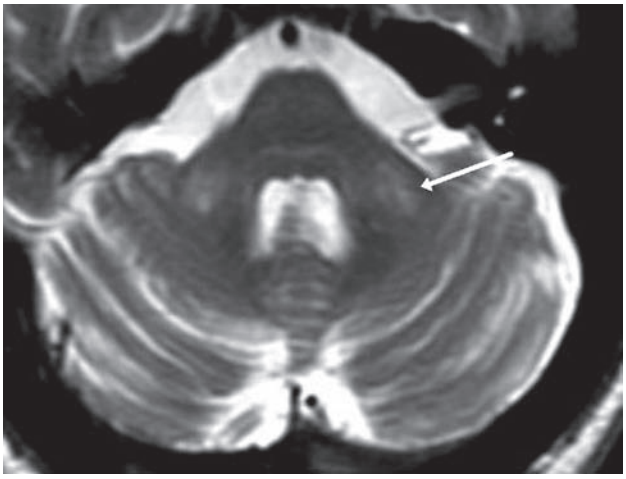

Figure 4 Fragile X tremor/ataxia syndrome. Medial cerebellar peduncle high signal changes on axial T2-image.

- **Previous intracranial bleeding** may leave superficial siderosis with haemosiderin appearing as a black rim around the posterior fossa structures on gradient-echo or susceptibility-weighted MRI (figure 7).

Is alcohol the culprit?

Our patient drank 3–4 glasses of wine a day. There is often doubt as to whether ataxia might be alcohol-related. It is easier if there is a history of true alcohol abuse, but more commonly the patient drinks just slightly more than average. There are no good data on the duration and quantity of alcohol consumption that cause long-term ataxia. Despite the lack of epidemiological data, alcoholic cerebellar degeneration is one of the most common sporadic ataxias, especially in middle-aged men. Nevertheless, we recommend a search for other causes of ataxia in patients who report drinking only moderately.

In patients with alcohol-related ataxia, the symptoms affect gait and lower limbs more than arms and speech, often also with signs of peripheral neuropathy. The ataxia can stabilise or even improve with stopping alcohol, but worsen in those who continue.[4 5] Brain imaging typically shows vermis atrophy.

Alcohol is directly toxic to the cerebellum, causing degeneration of the anterior superior vermis and hemispheres.[6] This is worsened by associated vitamin B_1 deficiency, resulting from both a poor diet and a direct toxic effect on vitamin B_1 metabolism. Alcohol impairs thiamine uptake from the gastro-intestinal tract, reduces thiamine-dependent enzyme activity and depletes liver thiamine stores.[7] Severe vitamin B_1 deficiency causes Wernicke's encephalopathy,

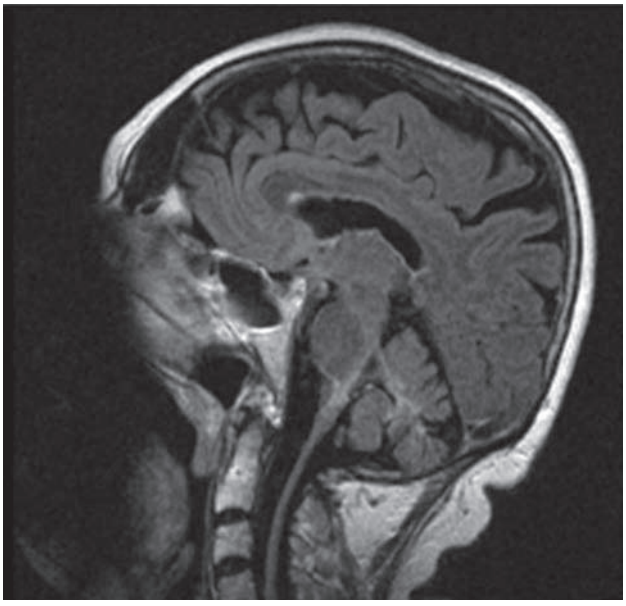

Figure 5 Alexander disease. Sagittal fluid attenuated inversion recovery images showing atrophy of cerebellum, brainstem (except pons) and spinal cord, and high signal changes within the cerebellar and brainstem white matter.

presenting the classical triad: encephalopathy, oculomotor dysfunction and gait ataxia. It is a neurological emergency, requiring urgent vitamin B_1 replacement.[8]

What about the other acquired causes? Should I really do a screen for malignancy?

We will not address the structural lesions further, as these will be apparent on the 'obligatory' initial MRI brain scan. However, there are some other acquired causes, which we discuss in order of their speed of onset.

Acute onset

(Para)infectious cerebellopathy is more common in children than in adults. Typically, there is a prodromal infectious phase, often caused (in adults) by the Epstein–Barr virus, followed by subacute cerebellar symptoms. The prognosis is usually good.[9]

In Miller Fisher syndrome, a variant of acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome), the triad of ophthalmoplegia, areflexia and ataxia develops over 1–2 weeks. The cause is molecular mimicry relating to antecedent infections, for example, *Campylobacter jejuni*. Serum anti-GQ1b antibodies are commonly elevated.[10] The treatment is with intravenous immunoglobulins or plasma exchange; the outcome is similar with either, with a trend towards a faster recovery after plasma exchange.[11]

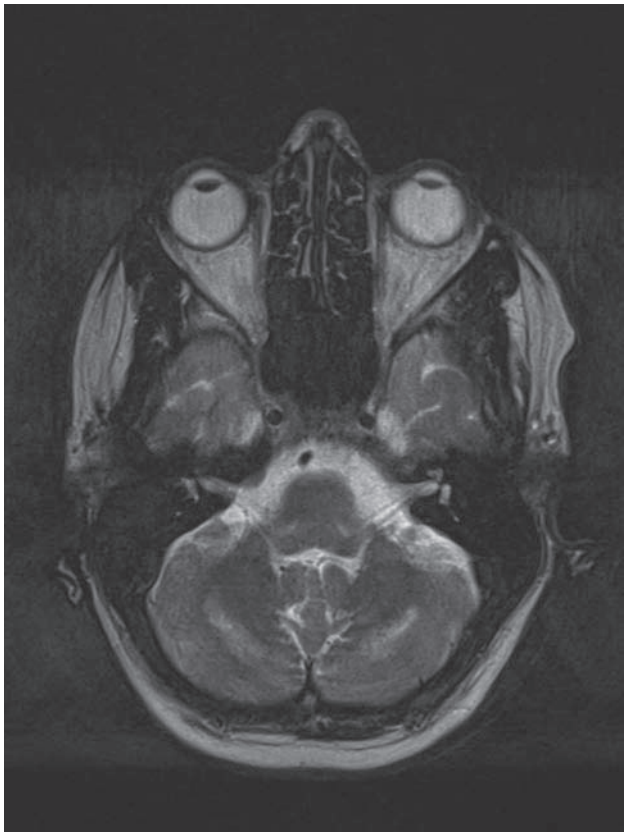

Figure 6 Polymerase γ. Symmetric, high signal changes in the cerebellar white matter dorsally from the dentate nucleus on axial T2-weighted MRI.

Subacute onset

1. SREAT—formerly Hashimoto's encephalopathy—gives ataxia progressing over weeks, with cognitive disturbance, myoclonus, seizures and ataxia. Patients have high serum thyroperoxidase antibody levels, although thyroid function is normal in half of the cases. The mean age at onset is 45–55 years, and it is five times more common in women than in men. Patients often have other autoimmune disorders, for example, type 1 diabetes mellitus and Sjögren's syndrome. It is readily treatable and improves dramatically with corticosteroids; in fact, the steroid response is a prerequisite for the diagnosis. The sooner treatment is started, the better the outcome.[12]
2. Creutzfeldt–Jakob disease is another rapidly progressive disorder with cerebellar ataxia. Sooner or later, patients develop a plethora of other neurological signs, including dementia, myoclonus and Parkinsonism. It is difficult to make the diagnosis very early. There are some suggestive MRI features (see above). Cerebrospinal fluid (CSF) often shows 14-3-3 protein and increased tau levels. The EEG typically shows periodic synchronous biphasic or triphasic sharp wave complexes.[13 14] Patients usually die within a year.
3. Paraneoplastic cerebellar degeneration also progresses over weeks. When suspected, patients

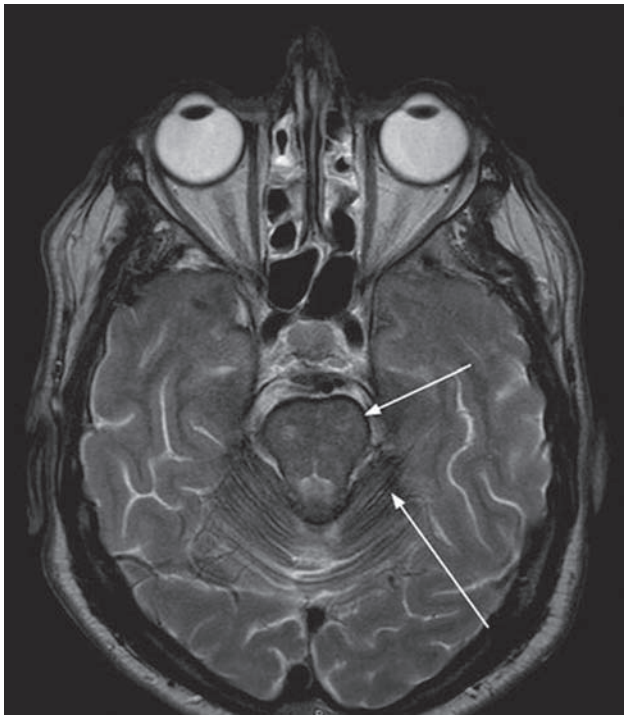

Figure 7 Superficial siderosis. Low signal changes around the pons and between the cerebellar foliae, reminiscent of haemosiderin deposits, on T2*-weighted gradient-recalled echo.

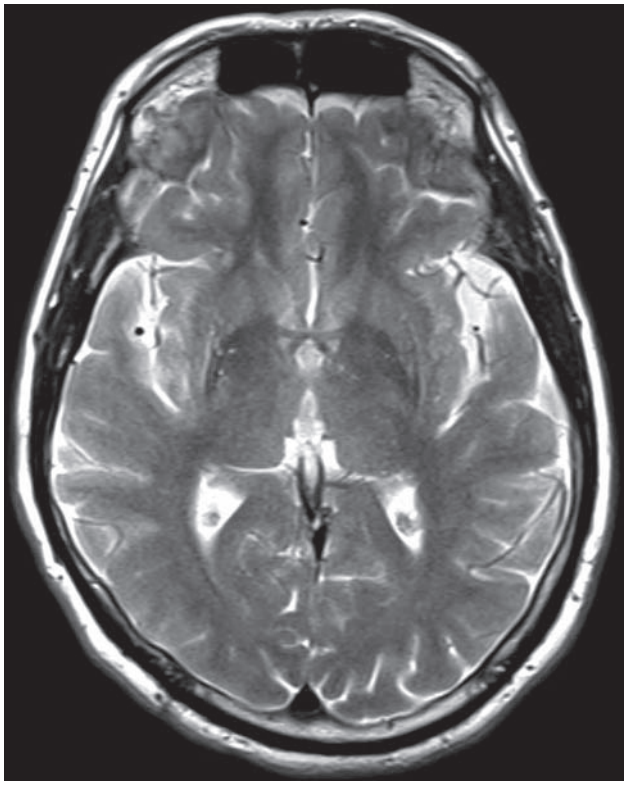

Figure 8 Cerebellar variant of multiple system atrophy. Hyperintense line lateral from the putamen (putaminal rim), particularly on the right on axial T2-image.

need additional imaging to identify an underlying malignancy, for example, mammography, testicular or ovarian ultrasound, CT scan of chest and abdomen, or whole-body positron-emission tomography scan. However, paraneoplastic syndromes can develop in the early stages of a malignancy, and so it might be difficult to demonstrate the tumour. If the initial screening is negative, repeat screening is advisable every 6 months for 4 years.[15] Brain MRI is often normal in the first weeks, but cerebellar atrophy develops over the subsequent months. The top four malignancies associated with paraneoplastic cerebellar degeneration are small cell lung cancer, breast cancer, ovarian tumour and Hodgkin's lymphoma. Like other paraneoplastic syndromes, these conditions are probably caused by cross-reacting humoral or cellular immune responses. Antineuronal antibodies can be tested for, but their low sensitivity means that a negative result does not exclude the diagnosis. Treating the underlying tumour, combined with immunomodulatory treatment, might improve or stabilise the symptoms, but for most people the prognosis is poor; up to 80% of patients never again walk unaided.[16] Previous reports suggested that the interval between onset of ataxia and tumour detection may be up to 4 years; there is thus uncertainty whether to perform a tumour screen and antineuronal antibody testing in all patients with ataxia starting from the last 4 years. The clinical context is paramount here, with the more rapid progression more likely associated with underlying malignancy.

4. Ataxia associated with anti-GAD antibodies also has an inflammatory cause. It is more common in patients with type 1 diabetes mellitus and in women. There is no proven best treatment, but corticosteroids and immunoglobulins occasionally improve the symptoms.[17]

Chronic onset

1. Coeliac disease may be complicated by neurological features including peripheral neuropathy and cerebellar ataxia. The ataxia is caused by inflammatory changes in the cerebellum. However, there is debate whether the so-called 'gluten ataxia' exists. This is a sporadic, otherwise unexplained cerebellar ataxia where the patient has coeliac-associated autoantibodies (antigliadin, antiendomysium and antitissue transglutaminase). There is a broad range of age at onset and usually no other specific signs. Most patients have no bowel symptoms or abnormalities on intestinal biopsies, and so no features of definite coeliac disease. Some authors claim that gluten ataxia could be the most common sporadic ataxia. The controversy is mainly due to these antibodies being also found in both hereditary ataxias and healthy controls.[18] Rather than causes, these antibodies might be a non-specific marker of another neuroinflammatory disease or an epiphenomenon triggered by the degeneration.[19] It is important to settle this issue since some patients appear to improve on a gluten-free diet. Although

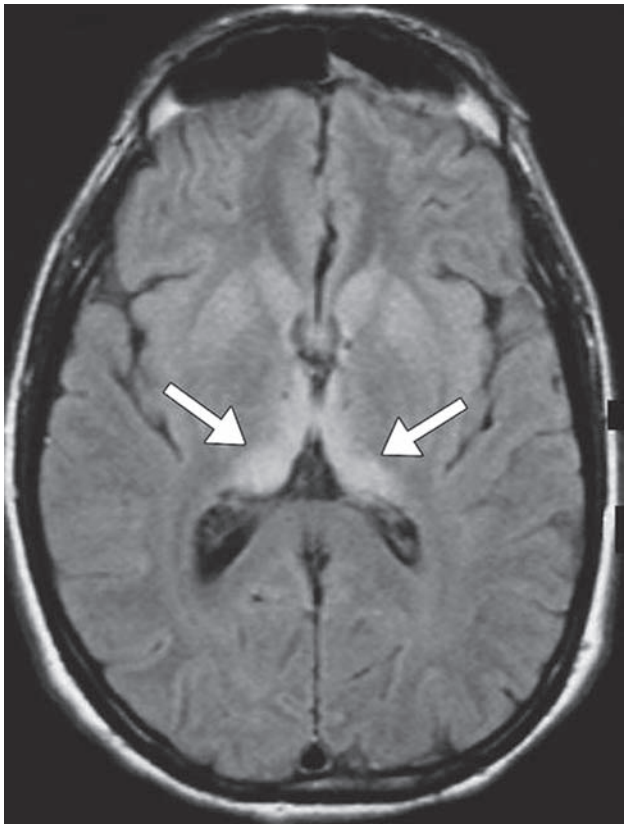

Figure 9 Creutzfeldt–Jakob disease. High signal changes on axial fluid attenuated inversion recovery image with the pulvinar (arrow), head of caudate and putamen.

we screen for these antibodies in patients with sporadic cerebellar ataxia, the yield in our unit has been extremely low. If positive, we openly discuss the controversy of this diagnosis with the patient, and jointly decide whether or not to try a gluten-free diet for about 6 months.

2. Superficial siderosis is a rare disorder characterised by cerebellar ataxia, with sensorineural deafness, pyramidal signs and dementia.[20] The age of onset age ranges between 14 and 77 years. Neuronal damage results from the deposition of free iron, ferritin and haemosiderin following repeated subarachnoid bleeding from either vascular malformations or previous brain surgery or trauma.[21] The typical MRI pattern is of a black rim around posterior fossa structures (see figure 7). CSF shows xanthochromia with siderophages. Removal of the bleeding source is the only effective treatment; iron chelation and CSF shunting do not help.[22]
3. Medication-induced ataxia may occur with several drugs, including antiepileptics (particularly phenytoin, carbamazepine and gabapentin), metronidazole, amiodarone, some anticancer drugs and pregabalin.
4. Metabolic causes of cerebellar ataxia are worth excluding by measuring serum vitamin levels (E and B), liver enzymes and (para)thyroid function.[23 24]

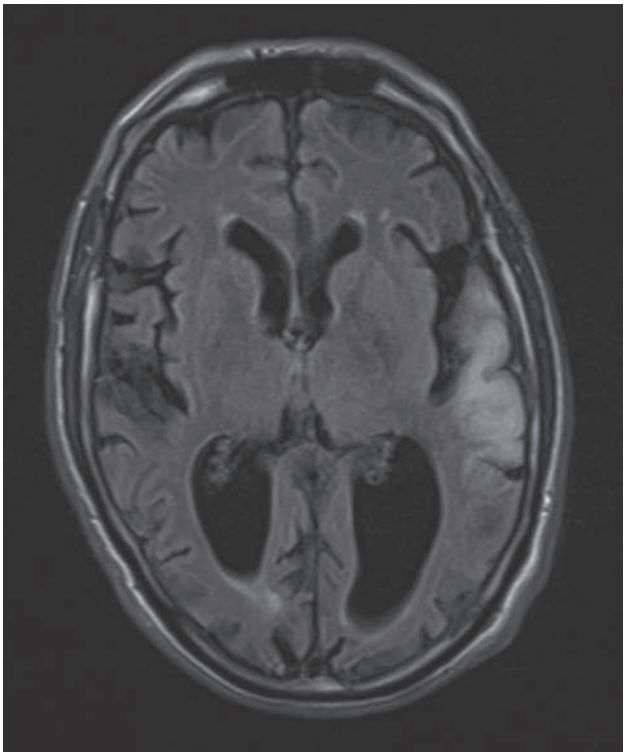

Figure 10 Mitochondrial encephalomyopathy, lactate acidosis and stroke-like episodes. Recent cortical infarction on axial fluid attenuated inversion recovery image.

5. Low-grade infections or other inflammatory causes should be searched for by CSF examination if progressive adult-onset ataxia remains unexplained after the above investigations.

Case follow-up

Besides ataxia, our patient reported urinary urgency and had pyramidal features. These also occur in many cerebellar disorders due to spinal cord involvement. The cerebellar atrophy and slow progression suggested a degenerative process. Routine blood tests were normal, including the gluten sensitivity screen. Alcohol excess seemed an unlikely cause.

Beware of MSA

The Parkinsonian variant of MSA is more common than the cerebellar variant worldwide, apart from Japan. MSA is an important cause of sporadic cerebellar ataxia, although the diagnosis is usually not made at the first visit. The onset peaks at between 50 and 70 years of age, although MSA can start as early as the fourth decade. The disease course is the giveaway, as other features soon appear, devastating quality of life and independence. Median survival is less than 10 years. Autonomic failure is prominent, with urinary incontinence, erectile dysfunction in men and postural hypotension; in retrospect, its onset often precedes the ataxia. Other features include Parkinsonism, pyramidal

Table 2 Symptom treatment options

Symptom	Drugs
Ataxia	Low dose benzodiazepines
	Riluzole
	Buspirone
	Amantadine
	Acetazolamide
	5-Hydroxytryptophan
Parkinsonian features	L-dopa
	Dopamine agonists
Cerebellar tremor	Propranolol
	Primidone
	Clonazepam
Nystagmus	Baclofen
	Gabapentin
	Clonazepam
	3,4-diaminopyridine
Dystonia	Botulinum toxin injections
	Anticholinergics
Muscle cramps	Magnesium
	Benzodiazepines
	Quinine
	Mexiletine
Spasticity	Baclofen
	Tizanidine
	Benzodiazepines
	Botulinum toxin injections
Urinary urgency	Spasmolytic agents
	Adrenergic α- receptor blockers
Restless legs	Dopamine agonists
	L-dopa
	Opioids
	Clonazepam

signs, antecollis, Pisa syndrome, facial dystonia, cold hands and feet, rapid-eye movement sleep behaviour disorder, inspiratory sighs, nocturnal stridor, a high-pitched quivery voice and polymini-myoclonus.

Online supplementary table S1 gives the revised consensus criteria. Clinically, we can only diagnose probable MSA: definite MSA requires neuropathological confirmation of α-synuclein deposits in glial cells.[25] Probable and possible MSA differ in the severity of their autonomic disturbance. Features supporting possible MSA (besides ataxia) are stridor, pyramidal signs and basal ganglia involvement (inferred either clinically from Parkinsonism or radiologically by structural or functional imaging). MR brain scanning may show not only the cerebellar and brainstem atrophy but also the 'hot cross bun' sign or a 'putaminal rim' (figure 8).

Idiopathic late-onset cerebellar ataxia is the diagnosis of exclusion, having excluded relevant causes in a patient with cerebellar ataxia (including genetic ones, see below). One can debate where early-onset cerebellar ataxia ends and idiopathic late onset cerebellar ataxia begins; therefore, some prefer the term 'sporadic adult-onset ataxia'. This is clearly an aetiologically heterogeneous group and an important reason for long-term follow-up is to identify 'conversion' to MSA that may occur later.[26]

Could this be genetic?

A negative family history, even done properly, does not exclude a genetic cause. Patients with sporadic ataxia may particularly have recessive disorders, but also occasionally dominant, X linked and mitochondrial diseases.

There have been recent major advances in the molecular genetics of ataxia. Online supplementary tables S2 and S3 provide an overview of the known dominant and recessive genes, and there are excellent reviews for more details on these genetic ataxia variants.[27 28] Below, we only briefly touch upon the genetic ataxias, focusing mainly on those presenting at later ages.

Dominant inheritance

The term 'spinocerebellar ataxias' (SCAs) is used synonymously with dominant ataxias. However, other ataxias with a dominant inheritance include dentatorubropallidoluysian atrophy and the episodic ataxias; there are also conditions where ataxia is one feature, such as Alexander disease, hereditary prion disease and neuroferritinopathy.

There are already over 30 different SCA types and SCA-36 is the most recent. The most common SCA subtypes are those caused by an expanded coding repeat, but there are non-coding expansions and conventional mutations in some of the other subtypes.[27] Age at onset is typically 30–40 years, but some SCA types occur much later (particularly SCA-6) and there are infantile cases (SCA-2 and SCA-7). The clinical picture ranges from isolated cerebellar ataxia to complex neurological multisystem diseases. Non-cerebellar features such as pyramidal features, peripheral neuropathy and movement disorders are very common, and are even the presenting or dominating feature. The clinical overlap between SCAs[29] makes it impossible to predict the underlying genotype accurately. Thus, when there is a dominant family history, we have to test for many SCA genes. There are some exceptions (see online supplementary table S2);

for example, if there is severe visual loss, SCA-7 is top of the list and if there is chorea, consider SCA-17.[30 31] The patient's ethnic origin is also helpful; for example, SCA-12 occurs mainly in India and SCA-10 in Latin America. SCA-3, although the most frequent subtype worldwide, is rare in the UK and Italy.

Recessive inheritance

Recessive disorders tend to have an early age at onset (below 20 years) and a complex, multisystem phenotype. However, occasional recessive ataxias present (much) later and/or are purely cerebellar.

Several childhood conditions can present later, including Friedreich's ataxia, ataxia with oculomotor apraxia types 1 and 2, ataxia telangiectasia, autosomal recessive cerebellar ataxia type 1, Tay–Sachs disease, Sandhoff's disease, cerebrotendinous xanthomatosis and Refsum's disease. These recessive ataxias often show an additional peripheral neuropathy.[32]

Friedreich's ataxia is the best known and most prevalent recessive ataxia. The classical phenotype starts before the age of 20 years with progressive cerebellar and sensory ataxia, absent deep tendon reflexes and extensor plantar responses. Additional features include cardiomyopathy, diabetes mellitus, scoliosis and foot deformities.[33] It is caused by intronic GAA repeat expansions in the FXN gene. About 25% of FXN mutation carriers have an atypical phenotype, such as late onset, for example up to 64 years. In such very late-onset cases, there is often both ataxia and spastic paraparesis (spastic ataxia).[34]

Ataxia telangiectasia also may have atypical forms. The cerebellar ataxia can manifest after the age of 30 years, but often there is already a previous (unexplained) extrapyramidal syndrome, comprising chorea, dystonia or a resting tremor. Conjunctival telangiectasias and oculomotor apraxia can develop. There may be a raised serum α-fetoprotein level. It is important to diagnose ataxia telangiectasia promptly because patients may develop mainly haematological malignancies, even in those with atypical forms.[35]

Adult-onset ataxia with oculomotor apraxia type 1 has a different phenotype from the more common, juvenile onset form. Here, oculomotor apraxia and chorea can be absent, with the core phenotype being only cerebellar ataxia and axonal neuropathy. A mutation in the APTX gene is diagnostic, but other laboratory findings include low serum albumin, high cholesterol and high serum creatine kinase.[36]

X linked inheritance

There are few X linked forms of inherited ataxia, of which the FXTAS is the most important. This syndrome is caused by premutations (55–200 CGG repeats in the FMR1 gene, the same gene that causes fragile X when there is a full mutation (>200 repeats)). It predominantly affects men aged over 45 years and leads to action tremor, cerebellar ataxia and behavioural changes, and sometimes Parkinsonism, peripheral neuropathy, cognitive decline and autonomic dysfunction. Screening for this mutation in cohorts of (mainly male) patients with sporadic, unexplained ataxia identifies mutation rates of 0–4%. Additional clues are a family history of learning disability in boys or premature ovarian failure in women; MR brain scan shows T2-hyperintensities in the middle cerebellar peduncles (the MCP sign) in 50–60% of FXTAS patients. There have been reports of female FXTAS patients.

Mitochondrial inheritance

Mitochondrial disorders are caused by mutations in the mitochondrial DNA itself or in the nuclear genes controlling mitochondrial function. They generally have multisystem involvement, including central and peripheral nervous system, eyes, heart and endocrine glands. Cerebellar ataxia is common in many mitochondrial diseases, particularly in mitochondrial encephalomyopathy, lactate acidosis and stroke-like episodes (MELAS; figure 10), myoclonic epilepsy and mitochondrial myopathy with ragged-red fibres (MERFF), neurogenic muscle weakness, ataxia and retinitis pigmentosa (NARP) and mitochondrial disease due to POLG mutations.[37]

Often, other features or a family history makes one suspect a mitochondrial disorder, which then means in-depth investigations that often include a muscle biopsy.[38]

POLG is a nuclear gene coding for polymerase γ, which is involved in the maintenance of mitochondrial DNA. The POLG phenotype is very varied and includes (among others) Alpers' syndrome, chronic progressive external ophthalmoplegia, neuropathy, epilepsy and some movement disorders including myoclonus, Parkinsonism and cerebellar ataxia. Its ataxia–neuropathy phenotype seems to be associated with specific recessive mutations in this gene. Acronyms referring to this clinical constellation are mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO).[39] POLG syndromes can manifest after the age of 40 years,[40] and they may turn out to be the second most common recessive ataxia.[41]

Genetic screening

For patients with sporadic, pure cerebellar ataxia developing after the age of 45 years, screen for SCA-6, Friedreich's ataxia and FXTAS. If the family history is uncertain, consider analysing the other relatively common SCA genes. Other features may suggest the need to extend the genetic testing, for example, SPG-7 if there is spasticity or SCA-17 if ataxia is combined with chorea.

Patients with sporadic ataxia developing in their 30s need a more extensive investigation to also detect recessive disorders with a later onset age. With this onset age group, it is important to identify non-cerebellar signs which may refocus investigations, for example, cataract in cerebrotendinous xanthomatosis or demyelinating neuropathy in Refsum's diseases. If there is no distinctive phenotype, this could largely be covered by adding specific blood tests (see table 1) and a metabolic screen.

Case follow-up

In our patient, mutation analysis of the CACNA1A gene was positive, with 22 CAG repeats on the expanded allele. The final diagnosis was therefore SCA-6.

Neat diagnosis, now what?

Specific interventions

There are interventions and treatments for some acquired and even genetic ataxias, which can improve or stabilise ataxia, or prevent further complications.

These include:

- in toxic ataxia, stopping alcohol or the offending drug;
- in gluten ataxia and Refsum's disease, making specific dietary restrictions;
- in autosomal recessive ataxia with vitamin E deficiency, starting vitamin E supplements;
- in patients with SREAT or ataxia associated with anti-GAD antibodies, starting corticosteroids;
- in paraneoplastic cerebellar degeneration, treating the underlying tumour and starting immunomodulatory drugs;
- in cerebrotendinous xanthomatosis, giving bile acid replacement;
- in Friedreich's ataxia, prescribing idebenone to reduce cardiac hypertrophy.[32]

Symptom management

For most other causes of cerebellar ataxia, there is no specific treatment. Treatment of symptoms is therefore very important, as well as offering supportive care and trying to prevent complications. Some medications, for example, amantadine or riluzole, might help ataxia, but there are no good quality studies examining this benefit.[42–44] There are also medications for some other disease manifestations, for example, nystagmus, spasticity, Parkinsonism and urinary urgency (see table 2).

Physical interventions

There is increasing evidence for physiotherapy benefiting patients with ataxia.[45] Treatment should focus on gait and balance training and on prevention of falls, as these are very common in ataxia patients.[46] A speech therapist can help patients with dysarthria and swallowing difficulties to slow down articulation, to assume a certain posture during swallowing and to suggest types of food that are more easily swallowed. An occupational therapist can advise on walking aids and on adjustments to be made at home.[47]

A neurologist who is not familiar with genetic testing or counselling should refer the patient to a clinical geneticist if suspecting a genetic ataxia. Requesting, interpreting and discussing DNA testing is a delicate issue, with many potential caveats within the whole process.

Key points

- Careful clinical evaluation is essential to guide investigations; these should be targeted first at structural lesions and treatable conditions.
- Many treatable causes are inflammatory and progressive; do not blame alcohol too quickly.
- Many ataxias turn out to be degenerative: in chronic cases, consider genetic testing even without a family history, and follow-up in non-genetic cases looking for multiple system atrophy.
- Having excluded a treatable disorder, follow-up the patient to identify treatable symptoms and refer appropriately to allied healthcare workers.

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