

Figure 1: Aggregated data showing ethnic differences in SCA subtype frequency among families with ADCA.

in variable frequencies of the different subtypes both geographically and ethnically. SCA1, SCA2 and SCA3 are the commonest cause of ADCA in Caucasian families, but SCA3, SCA6 and DRPLA are more common in Asian populations (Figure 1).

A clinical classification of autosomal dominant cerebellar ataxia (ADCA) was introduced by Harding in 1982,<sup>14</sup> with a division into ADCA I, II and III based on the presence of extracerebellar features, a pigmentary retinopathy or a pure cerebellar syndrome respectively. Whilst this classification is still useful in clinical characterisation and can help with an increasing choice of diagnostic tests, it has now been superseded by a genetic classification based on the underlying genetic disorder (Table 3). Most of the SCA mutations identified to date are dynamic repeat expansions and many, but not all, are expanded triplet repeats. The majority are CAG repeats encoding a poly-

Table 2: Diagnostic strategy in late-onset cerebellar ataxia

First-line investigations
Magnetic resonance (MR) imaging of brain
Chest radiography
Electrocardiogram
Vitamin B1, B12
Thyroid function tests
Serum VDRL
Second-line investigations
Lumbar puncture (inc. oligoclonal bands, VDRL)
Genetic investigations – see Table 4
Anti-neuronal antibodies – see Table 6
Nerve conduction studies and electromyography
Investigations with specific indications
Serum copper, caeruloplasmin, 24 hour urinary copper
Blood film for acanthocytes
Serum lipids, immunoglobulins
Vitamin E levels
Phytanic acid levels
Very long chain fatty acids
Serum gonadotrophins
Serum hexosaminidase A
$\alpha$ -fetoprotein
Serum/CSF lactate
Muscle biopsy
Organic acids, ammonia, pyruvate
Anti-gliadin antibodies

lutamine track in the resulting protein leading to abnormal protein conformation; others are either untranslated repeats, deletions or missense mutations. The five main pathogenetic mechanisms of inherited ataxias are abnormal protein folding (e.g. SCA1), mitochondrial (e.g. Friedreich's ataxia), defective DNA repair (e.g. ataxia telangiectasia), channelopathies (e.g. EA1) and metabolic (e.g. inherited vitamin E deficiency).<sup>15</sup>

### Which genetic tests?

NHS laboratories across the UK commonly perform SCA1, SCA2, SCA3, SCA6 and usually SCA7 in response to a generic 'SCA screen' request. Other investigations such as SCA12, SCA17, DRPLA, and Friedreich's are available but usually must be specifically requested. Research laboratories may offer additional tests (Table 3) if the clinical circumstances are appropriate. The choice of diagnostic tests should be guided by local knowledge of the common ataxia families, an insight into the prevalence of common SCA subtypes (Figure 1) within the ethnic group, and the presence of suggestive extracerebellar features (Table 4). However, phenotypic variability and overlap make clinical diagnosis difficult, and in most cases, screening for a range of diseases is necessary.

If there is a strong dominant family history, it is appropriate to screen for SCA1, SCA2, SCA3, SCA6 and SCA7 as part of first-line investigations. An important clue to the presence of a dominantly inherited trinucleotide repeat (TNR) disorder is anticipation, resulting in increasing severity and earlier age of onset through generations. However, even in sporadic cases, a routine screen is recommended since the presence of a dominant family history may be hidden by reduced penetrance (e.g. SCA17), marked anticipation (most notable in SCA7) or false paternity.

In sporadic cases, or if there is a history of consanguinity or affected siblings, testing for Friedreich's ataxia (FA) is essential. FA is the most common recessive cause of spinocerebellar ataxia, and traditionally this clinical diagnosis was limited to patients with an onset below the age of 25 with

Table 3: Summary of the SCA mutations. Adapted from reference 35. The designation SCA9 is reserved and has not been used.

† These tests may be available in research laboratories.

SCA subtype	Gene/protein	Phenotype	Mutation
<b>Diagnostic test commonly available in clinical practice</b>			
SCA1	ATXN1/Ataxin 1	ADCA I	CAG repeat
SCA2	ATXN2/Ataxin 2	ADCA I	CAG repeat
SCA3	ATXN3/Ataxin 3	ADCA I	CAG repeat
SCA6	CACNA1A/CACNA1A	ADCA III	CAG repeat
SCA7	ATXN7/Ataxin 7	ADCA II	CAG repeat
SCA12	PPP2R2B/PPP2R2B	ADCA I	CAG repeat
SCA17	TBP/TBP	ADCA I	CAG repeat
DRPLA	ATN1/Atraphin 1	ADCA I	CAG repeat
<b>Test not available routinely †</b>			
SCA5	SPTBN2/ $\beta$ -III spectrin	ADCA III	Deletion/missense
SCA8	KLHL1AS/Kelch-like 1	ADCA I	CTG repeat
SCA10	ATXN10/Ataxin 10	ADCA I	ATTCT repeat
SCA13	KCNK3/KCNK3	ADCA I	Missense
SCA14	PRKCG/PRKCG- $\gamma$	ADCA III	Missense
SCA27	FGF14/FGF14	ADCA I	Missense
EA1	KCNA1/K <sup>+</sup> channel	EA	Missense
EA2	CACNA1A/PQ-type Ca <sup>2+</sup> + $\alpha$ -1A	EA	Missense
EA5	CACNB4/Ca <sup>2+</sup> channel $\beta$ 4	EA	Missense
EA6	SCL1A3	EA/Migraine	Missense
<b>Gene not yet identified or published</b>			
ADCA I: SCA11†, SCA15, SCA16 and SCA26.			
ADCA III: SCA4, SCA18, SCA19, SCA20, SCA21, SCA22, SCA23, SCA24, SCA25, SCA27 and SCA28			
Episodic: EA3, EA4			

**Table 4: Genetic investigation of adult-onset cerebellar ataxia. † Feature highly suggestive of diagnosis**

Indication	Possible Diagnoses
Recommended routine screen	SCA1, SCA2, SCA3, SCA6, SCA7, FRDA
Pure ataxia	SCA6 †
Slow ocular saccades	SCA1, SCA2†, SCA3, SCA7,
Ophthalmoplegia	SCA1, SCA2, SCA3
Pigmentary maculopathy / retinopathy	SCA7 †, abetalipoproteinaemia
Cognitive impairment	DRPLA†, SCA17 †, HD
Chorea	DRPLA†, SCA17, HD
FA phenotype	FRDA †, vitamin E deficiency, abetalipoproteinaemia, AT
Cataract	Mitochondrial, cerebrotendinous xanthomatosis
Oculomotor apraxia	AT, ataxia with oculomotor apraxia type 1+2
Epilepsy	DRPLA †, SCA10, SCA17, HD, Wilson's disease, mitochondrial, prion disease
Myokymia	SCA3, EA1
Myoclonus	DRPLA, SCA2, SCA3
Peripheral neuropathy	SCA1, SCA2, SCA3, SCA4†, SCA6, SCA12, SCA18 †, SCA22, SCA25 †
Pyramidal signs	SCA1, SCA2, SCA3 †, SCA7, SCA12
Extrapyramidal signs	SCA1, SCA2, SCA3, SCA12, SCA17, SCA21
Dystonia	SCA3, SCA17

progressive ataxia, absent lower-limb reflexes and skeletal abnormalities, often associated with additional non-neurological symptoms such as cardiomyopathy and diabetes mellitus. Since the identification of the expanded intronic TNR (GAA) in the X25 gene (94% of patients),<sup>16</sup> it is now known that the clinical spectrum is broader than that defined by classical criteria, and includes patients with disease onset over the age of 25 with retained tendon reflexes. The remaining 6% of patients are compound heterozygotes with an expanded repeat on one allele, and a point mutation on the other. FA is thought to be due to mitochondrial dysfunction; the gene encodes frataxin, a mitochondrial protein. Even in those patients without the characteristic phenotype, up to 5.2% of patients with sporadic ataxia may have FA and in those below the age of 40 this rises to 21%.<sup>13,17</sup> Other recessive disorders are listed in Table 5.

SCA1 is highly variable but a pancerebellar syndrome is usually described, with prominent ataxia of gait, limb, speech and eye movements. SCA2 is associated with marked ocular saccadic slowing. SCA3 is the most common subtype (Figure 1) and has a widely variable phenotype. SCA6 is commonly described as a late-onset pure ataxic syndrome. Pigmentary maculopathy and retinopathy is associated with SCA7, but this may be preceded by ataxia by up to 20 years.

There is much controversy regarding SCA8 and testing is not offered routinely since there is low penetrance and expanded repeats are also found in unaffected controls.

A history of psychiatric illness, chorea or dementia should prompt testing for DRPLA (dentatorubral pallidolusian atrophy), SCA17 and HD. DRPLA is a rare autosomal dominant, clinically heterogeneous neurodegenerative disorder, most commonly reported in Japan and rare in Caucasian populations. In Europe and the United States, there have been 153 patients reported in the literature since 1989, segregating in 20 families. However, a pure gait ataxia can precede the other manifestations by up to ten years making diagnosis challenging in the early stages of disease.<sup>18</sup>

Discrete episodes of ataxia are associated with the dominantly inherited episodic ataxias, caused by mutations in genes encoding voltage-dependent potassium (e.g. EA1) and calcium (e.g. EA2) channels. Episodes may last minutes in EA1 and hours to days in EA2. Interictal myokymia may be evident clinically and electromyographically in EA1, and some cases of EA2 can have a more progressive course similar to SCA6, to which it is allelic. Genetic testing is not widely available, and since EA2 may be responsive to acetazolamide, a therapeutic trial is warranted if the diagnosis is suspected clinically.

Fragile-X tremor/ataxia syndrome (FXTAS) was first described in 2001 in five elderly men carrying premutation range (55-200) triplet repeats in the FMR1 gene and characterised by a progressive action tremor associated with executive frontal deficits and generalised brain atrophy.<sup>19</sup> Initially thought to affect only men, it has subsequently been described in women albeit in a less severe form.<sup>20</sup> FMR1 premutation may account for 3.6–4.2%<sup>21,22</sup> of cases of sporadic ataxia in male patients older than 50

**Table 5: Additional diagnostic possibilities in young adults**

Disorder	Gene locus	Diagnostic features
<b>Autosomal recessive disorders</b>		
Friedreich's ataxia	X25-FRDA1 9q13-q21	Hyporeflexia Pyramidal signs Cardiomyopathy
Ataxia telangiectasia	11q22.3	Elevated $\alpha$ -fetoprotein Reduced serum immunoglobulins Telangiectasia, dystonia Predisposition to malignancy
Wilson's disease	13q14.3-q21.1	Reduced caeruloplasmin Elevated 24hr urine copper Kayser-Fleischer ring Hepatosplenomegaly Abnormal basal ganglia on MR
Abetalipoproteinaemia (acanthocytosis)	4q22-q24	Blood film for acanthocytes Serum cholesterol very low Serum beta lipoprotein absent. Pigmentary degeneration of the retina
Inherited vitamin E deficiency Refsum's disease (HMSN IV)	8q13.1-q13.3 10pter-p11.2, 6q22-q24	Reduced vitamin E levels Elevated phytanic acid levels Retinitis pigmentosa Polyneuropathy, sensorineural deafness Ichthyosis
Adrenoleukodystrophy /Adrenomyeloneuropathy	Xq28	Very long chain fatty acids Men (X-linked) Abnormal MRI brain
GM2 gangliosidosis	(multiple)	Reduced serum hexosaminidase A Supranuclear gaze palsy Dystonia
Cerebrotendinous xanthomatosis (Cholestanolysis)	2q33-qter	Elevated serum cholestanol Tendon xanthomata Dementia, cataract
Peripheral neuropathy Hypogonadotropic hypogonadism (Holmes syndrome)		Secondary sexual characteristics Loss of libido / infertility
<b>Mitochondrial and metabolic disorders</b>		Elevated serum / CSF lactate Elevated serum ammonia, pyruvate Muscle biopsy, organic acids Additional neurological sequelae (e.g. stroke, myoclonic epilepsy)

**Table 6: Antibodies to neuronal antigens in cerebellar syndromes.**  
Adapted from references 29, 36.  
(VGCC—voltage-gated calcium channel antibodies)

Antibody	Antigen	Typical tumour associated
Anti-Yo	<i>cd62,32</i> (purkinje cytoplasmic)	Gynaecological Breast
Anti-Hu	<i>HuD</i> (neuronal nuclear)	Small cell lung cancer (75-80%) Neuroblastoma
Anti-Ri	<i>Nova1,2</i> (neuronal nuclear)	Breast Small cell lung cancer
Anti-Tr	(purkinje cytoplasmic)	Hodgkin's Lymphoma
Anti-VGCC	VGCC	Small cell lung cancer (>80%)
Anti-GAD	GAD	None
Anti-Ma1	<i>Ma1,2,3</i> (neuronal nucleolar)	Various
Anti-Ma2	<i>Ma2</i> (neuronal nucleolar)	Testis

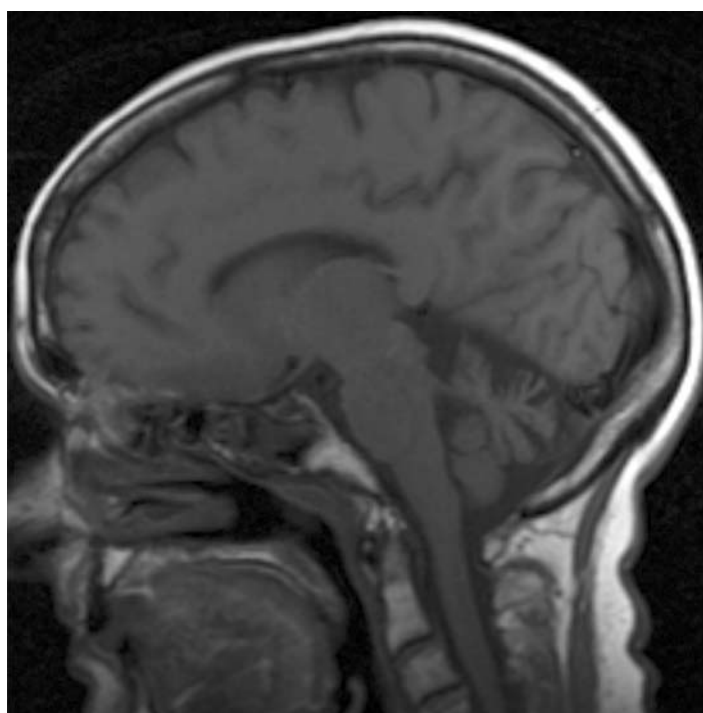


Figure 2: Pure cerebellar atrophy in SCA6.

years. FXTAS should be considered in elderly men, especially in families with grandchildren with Fragile-X or reported learning difficulties.

### Age of onset and disease progression

In young adults (<40 years), there are a wide range of important, potentially reversible or treatable diagnostic possibilities that should not be missed (Table 5). Fortunately, these diagnoses are normally suspected because of the presence of characteristic extracerebellar features. While an early onset is normally associated with autosomal recessive disorders, it does not preclude the presence of a dominantly inherited disorder and they should be considered in both sporadic and familial cases. The term 'idiopathic' late-onset cerebellar ataxia<sup>23</sup> is a diagnosis of exclusion. However, there is considerable overlap with other neurodegenerative disorders and within five years 29–33% of cases will meet diagnostic criteria for possible or probable multiple system atrophy (MSA).<sup>8,24</sup> The main features of MSA comprise autonomic failure, parkinsonism, cerebellar ataxia and pyramidal signs in any combination, with two major subtypes distinguished: MSA-P (80%) and MSA-C (20%) with parkinsonian or cerebellar features dominating respectively,<sup>25</sup> but ultimate confirmation of diagnosis is pathological. Patients with MSA have a poor prognosis and accumulate greater disability, remaining ambulant for a median of six years, and surviving only seven to nine years. This contrasts to those with a pure cerebellar syndrome whose median survival is over 20 years.<sup>24,26,27</sup> In patients over the age of 50, a rapidly progressive disease course should prompt re-evaluation for MSA.



Figure 3: 'Hot cross bun' sign in multiple system atrophy.

### Is imaging helpful?

Magnetic resonance imaging is essential in the diagnostic work-up of patients presenting with late-onset cerebellar ataxia. The most important benefit is the exclusion of an acquired cause, but it can also provide clues to other causes of sporadic and familial ataxia. There are three clear patterns of radiological abnormality:

- spinal atrophy,
- cortical cerebellar atrophy (CCA) and
- olivopontocerebellar atrophy (OPCA).

FA is characteristically associated with cervical spinal cord atrophy. CCA is found in the pure cerebellar syndromes (e.g. SCA6 - Figure 2) whereas OPCA is found in those with prominent extracerebellar features. There is considerable overlap between all the SCAs and imaging cannot be used for diagnostic purposes alone.

In MSA, cranial MR imaging may show non-specific OPCA, as well as putamen, caudate and basal ganglia atrophy. Signal hyperintensities in the pons and middle cerebellar peduncles may be seen on T2-weighted images to give rise to 'the hot cross bun sign' (Figure 3) but such changes are also found in some patients with proven SCA.<sup>28</sup> The presence of widespread brainstem, caudate and putamen atrophy in patients presenting with cerebellar ataxia should raise the suspicion of MSA and predict a guarded prognosis.

### What about immunological ataxia?

In subacute disease, up to 5% of cases may be associated with anti-neuronal antibodies (Table 6) and their presence should initiate a search for an occult neoplasm.<sup>29</sup> Paraneoplastic cerebellar degeneration may present months or even years before the appearance of the underlying tumour, but its significance in chronic disease is unclear.

There remains considerable controversy regarding the presence and significance of auto-antibodies in chronic progressive cerebellar ataxia. Antibodies to glutamic acid decarboxylase (GAD) are well described in patients with type I diabetes mellitus and stiff-person syndrome, but it has been suggested that anti-GAD antibodies may play a pathogenic role in cerebellar ataxia<sup>30</sup> and even be responsive to immunosuppressive therapy.<sup>31</sup> Controversially, anti-glial antibodies have been implicated in the pathogenesis of some sporadic cases of cerebellar ataxia in patients without gluten enteropathy.<sup>32</sup> The presence of such antibodies may reflect a high prevalence

of auto-immunity within this population but more research is needed before any definitive conclusions can be made regarding the pathogenic role of these antibodies in sporadic ataxia.

### Management

Early and accurate diagnosis is invaluable in guiding treatment, and providing patient counselling and support. However, in up to 80% of cases, even after extensive investigation, no definitive diagnosis is made. The diagnostic label 'idiopathic cerebellar ataxia' is unsatisfactory for both clinician and patient and in this group, longitudinal follow-up is essential to monitor progress and identify new symptoms and signs that may point to a previously neglected diagnosis. In symptomatic ataxia, management must be guided by the underlying cause, but all patients and their families need ongoing support. Local and national patient support organisations such as Ataxia UK (<http://www.ataxia.org.uk/>) can provide patient information leaflets, telephone advice lines and facilitate the creation of local patient groups.

Patients will also benefit from multidisciplinary care. In patients with FA, orthopaedic input

may be required for skeletal deformities and early referral to a cardiologist is essential for management of cardiomyopathy. In all forms of spinocerebellar ataxia, patients may benefit from physiotherapy to reduce spasticity, improve mobility and to provide walking aids. Speech and language assessment is essential for those with communication and/or swallowing difficulties. Urinary difficulties commonly occur as a result of spasticity or autonomic failure, and have a considerable impact on quality of life for both the patient and their carer. Desmopressin spray may help nocturnal polyuria, anticholinergics such as oxybutynin may reduce detrusor instability and urgency, and intermittent or permanent urinary catheterisation may be required if there is incomplete bladder emptying.

In up to a third of patients with possible or probable MSA, symptoms of bradykinesia may respond to levodopa but its effect may decline within years, and use may be limited by autonomic and dyskinetic side-effects.<sup>33</sup> Autonomic failure is frequently difficult to manage, but if disabling patients should avoid aggravating factors such as large meals, straining at toilet, alco-

hol and drugs, and are sometimes helped by the use of elastic stockings, head-up tilt of the bed at night, increased salt intake and fludrocortisone. The diagnosis of an inherited condition requires careful counselling for both patient and family, and referral to clinical genetics is usually appropriate. At present, there are no disease modifying therapies available for the inherited ataxias.

### Summary

- Adult-onset progressive cerebellar ataxia frequently poses diagnostic difficulties
- A proven genetic aetiology may be identified in half of all dominant families but only 1 in 10 sporadic cases.
- Genetic investigation of sporadic disease should include SCA1, SCA2, SCA3, SCA6, SCA7 and Friedreich's ataxia.
- Application of additional genetic tests in familial disease should be guided by local knowledge of ataxia families and the presence of extracerebellar features.
- Patients should be followed up for diagnostic, treatment and supportive purposes, ideally in a specialist ataxia clinic.

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