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Management of Ataxia: Guidelines on Best Clinical Practice

Ataxia
UK

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1. Introduction	<i>page 4</i>
2. Diagnosis:		
2.1	Presentation	<i>page 6</i>
2.2	Investigations	<i>page 9</i>
2.3	Genetics	<i>page 11</i>
3. Management		
3.1	Referrals	<i>page 12</i>
3.2	Reviews and follow-up	<i>page 14</i>
3.3	Symptomatic treatments	<i>page 15</i>
3.4	Disease modifying treatments	<i>page 18</i>
3.5	Clinical trials and research	<i>page 21</i>
3.6	Continuing care	<i>page 21</i>
4. Feedback	<i>page 22</i>
Appendix 1:	Ataxia expertise in the UK	<i>page 23</i>
Appendix 2:	Diagnostic tests for adults	<i>page 24</i>
Appendix 3:	Genetic tests	<i>page 25</i>
Appendix 4:	The autosomal dominant spinocerebellar ataxias (SCAs)	<i>page 26</i>
Appendix 5:	List of inherited ataxias	<i>page 27</i>
Appendix 6:	Research studies on medical interventions for symptom relief	<i>page 30</i>
Appendix 7:	Speech and language therapy – further information	<i>page 32</i>
References	<i>page 34</i>

This document aims to provide recommendations for healthcare professionals on the diagnosis and management of people with ataxia. Ataxia means ‘lack of coordination’ and it is a symptom of many conditions. These Guidelines focus on the progressive ataxias, and exclude disorders where ataxia is an epiphenomenon

of another neurological condition (see [Table 1](#)). They have been developed through extensive consultation with ataxia specialist neurologists and other healthcare professionals. These Guidelines are also supported by the patient support organisation, Ataxia UK. Common causes of ataxia are outlined in [Table 2](#).

Table 1: Conditions covered in these Guidelines

- **Hereditary ataxias** – including Friedreich’s ataxia, spinocerebellar ataxias and episodic ataxias (but excluding ataxia telangiectasia)
- **Idiopathic degenerative** – forms of progressive cerebellar ataxia of unidentified cause
- **Other neurological disorders** in which progressive ataxia is dominant symptom eg ataxia due to gluten sensitivity

Table 2: Causes of ataxia

- ▶ Vascular
- ▶ Traumatic
- ▶ Developmental
- ▶ Neoplastic / paraneoplastic
- ▶ Infectious
- ▶ Inflammatory (eg multiple sclerosis)
- ▶ Metabolic
- ▶ Toxic / drug-related (eg alcohol)
- ▶ **Hereditary**
- ▶ **Idiopathic degenerative**
- ▶ **Other neurological disorders**

Focus of these Guidelines

The progressive ataxias are generally thought to be rare neurological conditions, and are poorly understood by healthcare professionals. However, recent evidence suggests that the ataxias are more common than previously thought and may be

under-diagnosed (see [Box 1](#)). This highlights the importance of producing these Guidelines which are intended to increase awareness and understanding of these conditions, and lead to their improved diagnosis and management.

Box 1: Epidemiology of the ataxias

Epidemiological studies of the progressive ataxias in the UK are sparse. Results of further epidemiological studies in the UK are expected in the next few years.

Recent UK studies:

- Estimated prevalence: 1 in 12,500 adults with autosomal dominant cerebellar ataxia in the North East of England.¹
- Estimated minimum prevalence: 10.2 in 100,000 people with late onset cerebellar ataxia in South Wales.²

European studies:

- The most common inherited ataxia in the UK is Friedreich's ataxia, which is a recessively inherited condition that tends to be of early onset. Estimated prevalence of Friedreich's ataxia in studies before the availability of genetic tests: 1 in 50,000. A more recent study estimated a carrier frequency of 1 in 85 and a disease incidence of 1 in 29,000³.

These studies suggest that the prevalence of the progressive ataxias is higher than conditions that are generally better known such as Huntington's disease⁴ and motor neurone disease.⁵

The presentation of a patient with ataxia can be considered in many domains. The entity may be transient (eg following a viral infection in a child), episodic (eg in a patient with multiple sclerosis) or progressive (eg in Friedreich's ataxia, an inherited neurodegenerative disorder). Onset may be acute (eg in a patient with stroke) or slow (eg vitamin or thyroid deficiencies). Finally the age of onset should be considered: the types of disorders presenting with ataxia in children or young adults (frequently developmental, metabolic or inherited causes) tend to differ from those presenting in older people (vascular, neoplastic or neurodegenerative). The clinician therefore has to synthesise many aspects of the history in coming up with a differential diagnosis for an individual patient.

The family history is crucial in patients with ataxia, in view of the frequency with which genetic/inherited factors contribute to its causation. Almost all forms of genetic transmission are recognised, but generally speaking young-onset ataxias tend to be of autosomal recessive [AR] inheritance (eg Friedreich's ataxia) whereas the autosomal dominant [AD] ataxias tend to present in young adults and in early middle life. With AR inheritance there is a 1 in 4 risk of further siblings also being affected, but the parents of the patient whilst carriers of the mutated gene are themselves clinically unaffected. Parental consanguinity is sometimes identified. With AD transmission, one of the parents is likely to have similar clinical

characteristics, but especially if carrying an unstable triplet repeat containing gene may have much milder clinical features and also may themselves have presented at a later stage in their lives. In this category, sometimes paternal transmissions particularly tend to lead to dramatically reduced ages of onset and more severe clinical phenotypes in offspring. Mitochondrial disease may be an under-diagnosed cause of 'inherited' ataxia, but here the mechanisms of transmission may be complex- including only maternal transmission, AR and rarely AD. Premutations of the fragile-X gene may be a cause of adult-onset ataxia ('Tremor-ataxia syndrome'), and affects men and women.

Presenting symptoms and signs of ataxia are well known, and are usually attributable to dysfunction of the cerebellum or its connections. Patients complain of slurred speech, clumsiness, incoordination and unsteadiness. Rarely oscillopsia (due to nystagmus) is reported. The clinical signs of cerebellar dysfunction can be summarised as follows:

- Speech may be slurred (dysarthric) and have a staccato quality
- Extra-ocular movement testing may demonstrate horizontal gaze-evoked nystagmus, hypermetropic/hypometropic saccades and saccadic interposition (jerky smooth pursuit)
- The outstretched arms when displaced

show limb hypotonia and rebound phenomena

- Intention tremor
- Dysmetria or 'past-pointing'
- Dyssynergia
- Dysdiadochokinesis
- Gait ataxia and in extreme cases impaired sitting balance

Midline cerebellar disease may only be detected by testing walking, especially heel-to-toe or tandem gait. It is important to recognise that impairments in motor function and sensation (especially joint position sense) can mimic cerebellar ataxia. Romberg's sign may detect impaired joint position sense, but in some forms of (spino)cerebellar ataxia, the posterior column sensory modalities are also impaired.

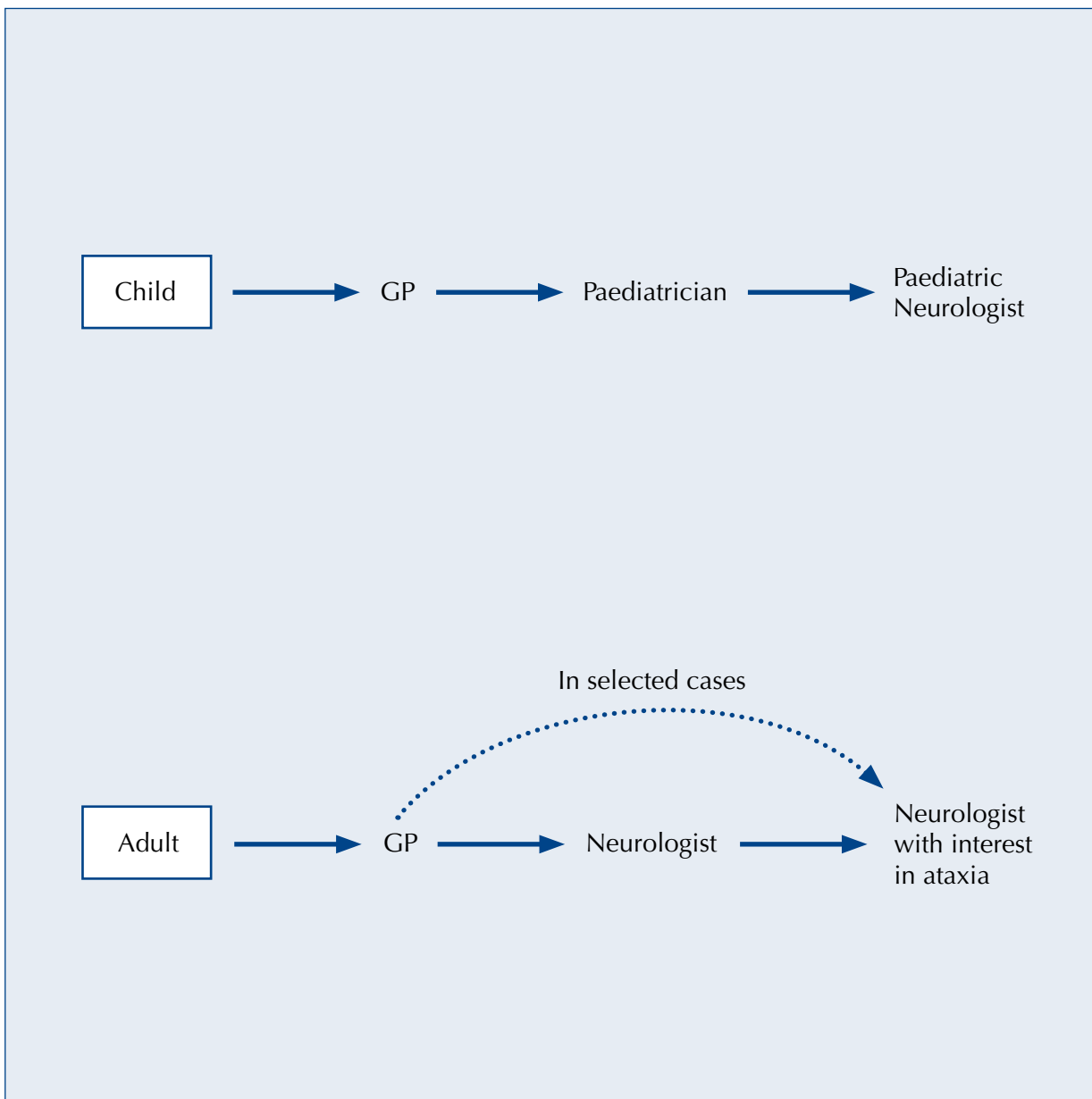
Ataxia may indicate neurological disease and should be referred without delay to secondary care.

Referral process

Patients suspected of having ataxia should be referred for secondary care. Depending on the clinical situation, this referral may need to be undertaken urgently. For example, in a case with a suspected tumour, this will have to be within 2 weeks.

In [Figure 1](#) (overleaf) the recommended referral processes for a child and an adult are shown. The patient should be generally seen in hospital by a paediatrician or neurologist. A referral to a centre specialising in ataxia is then recommended. In selected cases in adults it may be relevant for the GP to refer directly to the specialist neurologist (eg in cases where a diagnosis of a progressive ataxia has already been given).

Ataxia UK aims to accredit an increasing number of neurological centres across the country as recognised centres for the diagnosis and management of patients with ataxia. Ideally the transfer of patients within secondary care to the nearest recognised centre should take place speedily, when alternative diagnoses such as multiple sclerosis have been excluded. There has been a trend recently in UK acute Trusts to prioritise GP referrals over 'internal' referrals between hospital specialists. However we believe that where patients with ataxia are being referred internally, no such distinction should be made. A current list of Accredited Ataxia Centres and other recognised Ataxia Centres in the UK is found in [Appendix 1](#).

Figure 1: Referral pathways

When a diagnosis of progressive degenerative ataxia is made, referral to a specialist ataxia centre is recommended.

Adults

Details of appropriate investigations for adults are found in [Appendix 2](#). The tests are grouped in order of priority, as shown in the following table.

Table 1: Diagnostic investigations in adults

Primary care	Relatively inexpensive, common investigations, not specific for neurology, widely available; to exclude common (not necessarily neurological) conditions, which are sometimes easily treated. Could be ordered by GP prior to hospital referral.
Secondary care	<p>1st line MRI of the brain Rarer tests, usually ordered by neurologists; some conditions though rare are treatable (eg Wilson's); includes opinions of specialists eg ophthalmologists; basic genetic 'screen' especially if suspicious features eg family history.</p> <hr/> <p>2nd line Very rare and/or expensive investigations with low yield; rest of the testable genetic tests.</p>

Genetic tests

Clinical judgement is paramount in the application of tests. In certain instances the diagnosis may be so likely at the very first clinical encounter that a 'third line' genetic test, for example, may be undertaken immediately. Youngish patients with musculoskeletal

abnormalities, slowly progressive spinocerebellar ataxia with little or no nystagmus and absent reflexes should have the Friedreich's ataxia (*FRDA*) gene expansion(s) excluded early in second line investigations (along with insufficiency of vitamin E).

Children

The investigation of acquired ataxia in children is generally more urgent because of the necessity of excluding posterior fossa and brainstem tumours, and because of the likelihood that the cause

will be genetic and the parents may wish to have further children. Once ataxia has been noticed, an urgent referral to local paediatric services is necessary.

Table 2: Diagnostic investigations in children

1st Line	Neuroimaging is mandatory and a CT scan will exclude a tumour and may indicate a white matter disorder. If the CT is normal and the ataxia does not seem acute, local paediatric services should investigate in the light of clinical judgment and in consultation with the local tertiary paediatric neurology service.
2nd Line	Investigations likely to be available to local paediatric teams will include: full blood count; plasma lactate, urate, ammonia, very long chain fatty acids, amino acids, vitamin E, biotinidase and thyroid function; serum α -fetoprotein, immunoglobulins, thyroid antibodies and antigliadin antibodies; urinary vanillomandelic acid, uric acid and organic acids; and an ECG. Urgent referral to tertiary paediatric neurology services is almost always necessary to complete investigations and for advice about management.
3rd Line	Further investigations will include: magnetic resonance imaging of the brain and spinal cord; electromyography and nerve conduction studies; plasma and urine bile acids; whole blood acylcarnitine species; cerebrospinal fluid and simultaneous plasma lactate, glucose and amino acids; red cell purine nucleotide species; urine amino acids; white cell lysosomal enzymes, ubiquinone and chromosomal radiation fragility; FISH 22q and Angelman deletions; echocardiography; molecular tests for AT, AOAs and Nijmegen breakage syndrome; DNA for FRDA, common mitochondrial DNA mutations, SCAs and (importantly) to store. It might also be necessary to do more invasive investigations including skin, rectal, bone marrow and muscle biopsies.

For further information on the availability of diagnostic tests see [Appendices 2](#) and [3](#).

[Appendix 3](#) shows the currently available genetic tests, grouped according to modes of inheritance. Those underlined are available via the UK genetics testing network. Their website (www.ukgtn.org) gives details of accredited laboratories across the UK where the tests are undertaken, along with turnaround times. The others (ie not underlined) refer to cloned genes published in the international medical literature, but which are not available routinely as diagnostic tests. This document plans to make available (with regular updates) the details of (usually) research laboratories where such tests may be undertaken. This section will also be reviewed regularly to ensure that the list of identified genes is current: the total number of linked sites for AD SCA, for example, is around 28 currently, and in time the rest of the responsible genes will be cloned.⁶

With the AD spinocerebellar ataxias, the Harding classification considering these as types I, II or III is of some utility, and may inform genetic testing. Type I is so-called ‘complicated’ disease, where in addition to the ataxia, other neurological findings such as dementia, ophthalmoplegia, pyramidal signs and extrapyramidal features may be present. In type II disease there is progressive retinopathy and resulting blindness, and most cases to date have been associated with SCA7. Type III disease is reasonably ‘pure’ spinocerebellar ataxia. In [Appendix 4](#), the currently available AD ataxia genes are tabulated, and the corresponding Harding group and any especially distinguishing clinical characteristics are indicated. For a full list of inherited ataxias see [Appendix 5](#).

We consider genetic counselling to be a vital and integral component of ordering genetic studies, in view of the potential implications for the subject’s family members. The situation is simplest in the case of symptomatic subjects when the test is performed primarily for diagnostic purposes. However, it is important that the patient and any involved family members are informed about the potential implications, in case the test is positive. This level of information giving can be provided by neurologists, especially those with expertise in this field. The availability of Clinical Genetics services should be indicated to patients and their families. Indeed, it would be inappropriate to develop and offer this type of diagnostic service clinically without ready access to such specialists.

The situation is more complicated in the case of ‘at-risk’ subjects, where an individual is at that point clinically unaffected. There may also be approaches for pre-natal testing. In all of these situations, the individuals should be referred urgently to collaborating clinical geneticists, with all of the available data (including the genetic diagnosis of the index case, if the patient agrees to the release of this information). Good communication between the different specialties and professionals is vital.

Informed consent for research studies should also be sought when samples are obtained from patients and their families. Almost invariably the Ethics Committee submission in connection with the study will have clarified the appropriate consent to be obtained. Usually participants are given the option of being informed about any results that may emanate from studies, especially were this to be of relevance to them and their progeny.

Following the referral to a neurologist, in many cases it may be relevant to refer patients to other specialists.

Community Paediatric Multidisciplinary team

Children should be referred to the Community Paediatric Multidisciplinary team. All subsequent referrals and overall management is then coordinated by this team.

Cardiologist

Cardiomyopathy is often a feature of Friedreich's ataxia, therefore a referral to a cardiologist is required. Other ataxias are not normally associated with cardiological problems.

Neuro-ophthalmologist

Many of the ataxias are associated with eye problems, such as nystagmus or oscillopsia. A referral to a neuro-ophthalmologist is recommended as there are a number of treatments for these symptoms (see [Appendix 6](#)).

Neuropsychologist/Neuropsychiatrist

Some ataxias may be associated with cognitive problems, therefore in selected cases a referral to a neuropsychologist or neuropsychiatrist may be relevant. Examples of such ataxias are SCA1, SCA2, SCA3 and DRPLA. The absence of cognitive impairment is a useful distinguishing diagnostic feature, eg cognitive impairment has not been reported in Friedreich's ataxia or MSA. However, as in all patients with neurological disorders, patients with a progressive ataxia are susceptible to depression.

Neurological and spinal surgeon/orthopaedic surgeon

Patients with Friedreich's ataxia often develop scoliosis. Referral to neurosurgery and/or orthopaedic surgery may therefore be appropriate in some cases. Patients with Friedreich's ataxia may develop *pes cavus*, therefore referral to an orthopaedic surgeon with specialty in foot and ankle surgery may be appropriate.

Urologist

Bladder problems can be a feature of some of the ataxias. This occurs, for example, in multiple system atrophy. In later stages of various spinocerebellar ataxias, urinary incontinence is also sometimes experienced.

Neurorehabilitation

Patients would benefit from a referral for neurorehabilitation at the early stage of the disease in order to establish strategies to maintain function (eg balance, upper limb coordination, speech and swallowing).

Physiotherapy is often valuable, particularly to preserve mobility, and to avoid other problems, such as those associated with being in a wheelchair. Regular follow-up is important. Patients will also need advice on walking aids at the different stages of their condition. Referral to a wheelchair clinic for specialist seating advice is important at the appropriate stage of the disease.

Patients with progressive ataxia often experience dysarthria which, later in the disease, may cause communication

difficulties. A referral to a speech and language therapist (SLT) is therefore important. Dysphagia becomes more common as the disease progresses. Therefore this should also be assessed by a speech and language therapist.

(For more information on therapies see [Symptomatic Treatments section 3.3](#))

Ataxia patients benefit from regular assessments by an occupational therapist. Appropriate advice on home modifications and aids can help preserve independence as the condition progresses. Referral to social services may be appropriate for those patients who may need support for living with their condition.

Counselling

Anecdotal evidence has shown counselling to be beneficial in helping patients diagnosed with a progressive ataxia come to terms with their condition. The impact of diagnosis can be devastating⁷ and support from counselors at all stages of people's lives can be invaluable.

Patient Support groups

Referral to a patient support organisation is recommended. Ataxia UK provides support to people with all ataxias. The Sarah Matheson Trust provides support solely to people with multiple system atrophy, and the AT Society provides support to people with ataxia telangiectasia. When progressive ataxia is first diagnosed patients will often not have heard of the condition and will not know

anyone else with it. At this stage the support that can be provided by patient support organisations can be crucial. The possibility of meeting others in the same situation, receiving emotional support and information from a Helpline, finding out how others cope with the symptoms, can be of great benefit to people with ataxia. Although each support organisation provides its own services, many will also provide the opportunity for patients to be informed about research developments and take part in research projects.

Contact details:

- **Ataxia UK**

(registered charity number 1102391).
Winchester House, Kennington Park,
Cranmer Road, London SW9 6EJ.
www.ataxia.org.uk
Helpline: 0845 644 0606

- **Sarah Matheson Trust**

for multiple system atrophy
(registered charity number 1062308)
Pickering Unit, St Mary's Hospital,
Praed Street, London W2 1NY
www.msaweb.co.uk
Tel: 020 7886 1520

- **Ataxia Telangiectasia Society**

(registered charity number 1105528)
IACR-Rothamsted, Harpenden,
Herts AL5 2JQ
www.atsociety.org.uk
Tel: 01582 760733

Patients should be offered 6-12 monthly reviews from a neurologist. If it is difficult for patients to travel to the hospital, follow-up appointments could be less frequent. Regular follow-up reviews are important for a number of reasons. Firstly, it enables the neurologist to monitor the progression of the condition and identify any new symptoms that may need treatment. Secondly, if patients are discharged and not offered a follow-up appointment they are not likely to benefit from medical advances. For example, new diagnostic tests are regularly becoming available, especially

as new genes are identified, thus increasing the possibility of identifying a diagnosis for patients with idiopathic cerebellar ataxia. In addition, new treatments may be developed, both ones that may affect disease progression and for symptomatic relief.

Regular follow-up of patients with Friedreich's ataxia is necessary, specifically to monitor for the development of cardiomyopathy and diabetes. Annual ECGs/echocardiograms and urine/blood tests for diabetes are recommended.

THERAPIES

A full range of therapies should be available for patients with ataxia. These should include: physiotherapy, speech and language therapy, occupational therapy, dietetics, psychological support and support from social services.

Speech and Language Therapy (SLT)

Given that cognitive decline is not a prominent feature of the majority of the ataxias described in these Guidelines, language difficulties are generally not reported in these patients. Instead, any changes to communication will most likely arise from the direct effects of the cerebellar symptoms on speech muscle movement, as well as secondary or compensatory effects due to other aspects such as posture, fatigue, etc. In addition, dysphagia can become a problem due to muscle weakness and poor coordination of the oral and laryngeal musculature.

Speech problems

It is advisable for the SLT to see patients with degenerative disorders at early stages when speech problems are still mild, although many are not referred until their difficulties are more pronounced. Early referral can be helpful from a psychological / counselling point of view. In addition, there is some evidence that early practice will allow patients with degenerative disorders to maintain function for longer. If patients are seen at the initial stage, management should consist of providing information of common problems that might be experienced, general

advice on effective communication and, if appropriate, some self-practice exercises. An open self (re)referral system should be in place to allow patients to receive further therapy should the need arise at a later stage.

If patients are referred to SLT at a stage where direct input is required, a comprehensive diagnostic assessment should be carried out. This should focus on the primary speech impairments, as well as difficulties secondary to the experienced problems, eg pragmatics, communicative effectiveness, psychosocial impact etc. Other contributing factors such as depression need to be considered, and it might be appropriate to involve carers in the evaluation.

Treatment should aim to improve communicative effectiveness, either by direct management of the speech problem and/or through environmental adaptation. There is evidence from the Parkinson's disease literature that intensive treatment is more effective than weekly therapy, but the patient's individual needs must be taken into account in making this decision. If the speech problem becomes too severe, the use of Alternative and Augmentative Communication aids (AAC) should be considered.

Swallowing Problems

Dysphagia is a potential complication of the disease, particularly in the later stages when compensation for minor difficulties is compromised.⁸ Problems can occur in the oral and pharyngeal stages and, given the

complexity of the difficulties, patients should be referred to an SLT for detailed clinical assessment. The SLT might also consider the possibility of more detailed assessment using X-ray (Videofluoroscopy of Swallow). Depending on the outcome, it might be advisable to refer the patient on to a specialist multidisciplinary team, if the dysphagia needs to be managed jointly with other types of problems such as poor posture.

Care should be taken that patients with swallowing problems are well hydrated and maintain good oral hygiene to prevent a worsening of dysphagia or secondary symptoms such as oral infections. This is particularly important for those who have reached the non-ambulatory stage.

More advice on best practice in managing the disorder can be found in the sections relating to acquired motor speech disorders as well as progressive neurological disorders in *Communicating Quality 3* (2006), as well as the *RCSLT Clinical Guidelines* (2005).

For more information on speech and language therapy also see [Appendix 7](#).

Physiotherapy

Little is known about the current physiotherapeutic practice and the effectiveness of treatments. A review of physiotherapy practice in the UK is therefore planned and a supplement to this publication will then be produced.

Medical interventions

Patients with progressive ataxia can experience a variety of symptoms, some of which can be treated using medications.

The following symptoms can be treated with medications and therefore treatment should be offered:

a) Cardiac problems (ie cardiomyopathy)

A cardiologist can prescribe medications, where appropriate, to manage symptoms of cardiomyopathy.

b) Bladder problems

Some people with ataxia experience bladder problems. Although they cannot be cured, they can almost always be managed. A referral to a continence advisor is appropriate, and occasionally for special assessments/ treatments, referral to an urologist or gynaecologist may be needed.

With overactive bladders (presenting with urgency, precipitancy and urge incontinence) specific intervention with anti-cholinergic drugs (oxybutinin, propiverine, solifenacin, trospium) can be very helpful. In this situation, a post-micturition ultrasound scan of the bladder after the initiation of treatment or dose escalations would be recommended to exclude retention.

Practical advice on the avoidance of smoking, alcohol and caffeine-containing drinks should also be given, and in the occasional cases of

stress incontinence, referral for physiotherapy would be appropriate.

c) *Depression and other psychiatric symptoms*

Practical and effective treatment of symptoms of depression can be carried out in primary care, without the need for specialist psychiatric input. In addition to pharmacological interventions, counselling can offer significant benefits. In special cases, more input from secondary level psychiatric services may be indicated, especially if symptoms of dementia or psychosis are present.

d) *Contractures*

Referral to a physiotherapist and/or orthopaedic surgeon is appropriate. A review of the management of contractures can be found in the NICE Clinical Guidelines on the management of multiple sclerosis (November 2003).⁹

e) *Muscle spasms and spasticity*

Muscle spasms can be experienced by patients with ataxia, and there are effective treatments that can be prescribed.

A comprehensive review of the management of spasticity can be found in the NICE clinical guidelines on the management of multiple sclerosis (November 2003).⁹ There are no specific features of spasticity in people with ataxia, therefore it is advisable to follow the MS Guidelines.

There are no proven treatments for other symptoms so it is not possible to give specific recommendations. There is some evidence however for the efficacy of other medications from pilot clinical trials or expert experience. See [Appendix 6](#) for a summary of such studies.

Some forms of progressive ataxias are treatable; hence the importance of ensuring an accurate diagnosis is made quickly. For the majority of progressive ataxias there are no proven treatments.

Friedreich's ataxia

In the case of FRDA, as yet there are no large scale studies justifying the use of any agents to prevent progression, or the development of complications. However, given its prevalence, this is an area of active research interest. A number of small treatment trials have been carried out and others are in the pipeline. In the case of cardiomyopathy in FRDA, there have been small scale studies completed thus far that show modest benefits from idebenone therapy.¹⁰⁻¹⁵ Larger scale idebenone trials are underway in the US, UK and Germany to test the effect of idebenone on cardiomyopathy and also on neurological outcome measures. The effects of vitamin E and CoQ10 have also been tested in a small open trial and a larger double-blind controlled study. In the open trial the combination has shown the same benefit on cardiomyopathy as has idebenone and some provisional data on stabilising neurological dysfunction.¹⁶ Nevertheless, all prospective treatments for Friedreich's ataxia still need the benefit of large, probably multi-centre and international long term controlled studies.

Treatable progressive ataxias

Ataxia with Vitamin E deficiency

(See www.ncbi.nlm.nih.gov/omim/OMIM#277460; also see www.orpha.net/ORPHA96)

Patients diagnosed with Ataxia with Vitamin E deficiency (by having low serum Vitamin E levels in absence of fat malabsorption) should be administered vitamin E supplements. Studies have shown this leads to cessation of progression of neurological symptoms and mild improvement in certain patients, especially in the early stages of the disease.¹⁷⁻¹⁹

Patients who have Ataxia with Vitamin E deficiency often have similar symptoms with Friedreich's ataxia and this has at times resulted in misdiagnosis.

Wilson's disease

(See www.ncbi.nlm.nih.gov/omim/277900; also see www.orpha.net/ORPHA905)

Wilson's disease is an autosomal recessive inherited disorder of copper metabolism, resulting in pathological accumulation of copper in many organs and tissues. The leading neurologic symptoms in Wilson's disease are dysarthria, dyspraxia, ataxia, and Parkinsonian-like extrapyramidal signs. Symptoms may be fully reversible on treatment with zinc or copper chelators.²⁰

Ataxia with CoQ10 (ubiquinone) deficiency

(See Coenzyme Q10 deficiency [#OMIM 60742](http://www.ncbi.nlm.nih.gov/omim) or www.orphanet.net ORPHA35656)

Primary muscle coenzyme Q10 (CoQ10) deficiency is an apparently autosomal recessive condition with heterogeneous clinical presentations. Patients with these disorders improve with CoQ10 supplementation, hence the importance of early diagnosis. It has been observed in children as well as in adults with later onset cerebellar ataxia.^{21,22} The prevalence in the UK is currently unknown. Testing of CoQ10 deficiency can be performed on skeletal muscle samples or on blood mononuclear cells.²³ For details on testing see Appendix 2.

Gluten ataxia

Gluten ataxia is defined as a sporadic cerebellar ataxia associated with the presence of circulating antigliadin antibodies. This is a condition that has been defined in the last few years, and has been shown in a one-year placebo controlled trial to be responsive to a gluten-free diet.²⁴ The diagnosis of gluten ataxia is vital as it is one of the very few treatable causes of sporadic ataxia.

Cerebrotendinous xanthomatosis

(See [#OMIM 213700](http://www.ncbi.nlm.nih.gov/omim))

Cerebrotendinous xanthomatosis is a sterol storage disorder characterised by the accumulation of cholestanol and cholesterol in tendons, the central nervous system and in the bile. Treatment with chenodeoxycholic acid results in at least partial reversal of the neurological symptoms and in cognitive function in some patients. Early diagnosis and initiation of therapy is important.²⁵

Episodic ataxias

(See [#OMIM 160120](http://www.ncbi.nlm.nih.gov/omim) or www.orphanet.net ORPHA37612 for EA-1 and link to other episodic ataxias)

Some patients present with an episodic ataxia, mostly following a clinical diagnosis. Episodic ataxia types 1 and 2 are the most well known but other forms are being identified. In patients with episodic ataxia type 2 ataxic episodes can often be treated with the carbonic anhydrase inhibitor acetazolamide. Long term use is associated with the development of kidney stones as a side effect, hence preventative measures such as drinking citrus juices should be encouraged. As stress often triggers attacks, stress management techniques (eg meditation) can be helpful in controlling symptoms. Alcohol and caffeine should be avoided, and regular but modest exercise should be encouraged.²⁶

See [Appendix 6](#) for research studies on episodic ataxia types 1 and type 2.

Treatable causes of childhood ataxia

Some of the treatable conditions mentioned above can be seen in children. These include:

- Ubiquinone deficiency
- Episodic ataxia 2
- Familial vitamin E deficiency
- Cerebrotendinous xanthomatosis

In addition the following conditions are also treatable causes of childhood ataxia:

- Glucose transporter 1 deficiency
- Hypobetalipoproteinaemia
- Hartnup disease
- Biotinidase deficiency
- Pyruvate dehydrogenase deficiency

Glucose transporter 1 deficiency

(Glut-1 DS)

(See www.ncbi.nlm.nih.gov/omim/606777 and www.orpha.net/ORPHA71277)

Impaired glucose transport across the blood-brain barrier results in Glut-1 deficiency syndrome, characterised by infantile seizures, developmental delay, acquired microcephaly, spasticity, ataxia, and hypoglycorrachia. A ketogenic diet is found to be effective treatment.²⁷

For more information contact CLIMB (www.climb.org.uk)

Hypobetalipoproteinaemia

(See www.orpha.net/ORPHA426)

Hypobetalipoproteinaemia is a rare disorder characterised by low levels of fats, beta-lipoproteins and cholesterol.

For more information contact CLIMB (www.climb.org.uk)

Hartnup disease

(See www.ncbi.nlm.nih.gov/omim/234500; www.orpha.net/ORPHA2116)

Intermittent ataxia, psychotic behaviour and mental retardation are features of this condition. For more information contact CLIMB (www.climb.org.uk)

Biotinidase deficiency

(See www.ncbi.nlm.nih.gov/omim/253260)

Metabolic disorder characterised primarily by cutaneous and neurologic abnormalities. Can be treated with biotin. For more information contact CLIMB (www.climb.org.uk)

Pyruvate dehydrogenase deficiency

(See www.orpha.net/ORPHA765)

Metabolic disorder; for more information contact CLIMB (www.climb.org.uk).

3.5 Management – Clinical trials and research

It is good clinical practice to offer patients the opportunity to take part in research projects. For more information on research

developments and taking part in research projects contact Ataxia UK (www.ataxia.org.uk).

3.6 Management – Continuing care

For the majority of patients with ataxia, for most of the time, ongoing management can be provided at the primary care level. In addition to regular input from their GPs, other professionals including community therapists are likely to be involved. Specific community nursing needs may be delivered by district nurses. Travelling long distances to hospitals regularly may be difficult due to practical mobility issues or logistics (absence of public transport accessible for the disabled). Individual patients and their GPs need to decide for themselves what level of secondary (versus primary) care is required. The hospital-based neurologist/ataxia specialist will however remain involved as a coordinator and instigator of services. Effective communication between primary and secondary care is

therefore vital. We promote multi-disciplinary, multi-professional working practices that are mutually supportive, as recommended by the National Service Framework for long term conditions.²⁸

As ataxia is usually chronic and progressive, with the passage of time an even greater reliance on community services is likely. The establishing of durable networks of care at an early stage is therefore crucial. In line with recent recommendations in the National Service Framework for long term conditions, involvement of symptom and palliative care professionals is recommended,²⁸ especially as the disorder progresses. The remit at this stage may include providing practical and emotional support for carers, who are often family members.

We would like to update these Guidelines regularly, and would be keen to incorporate readers' ideas and experiences, especially examples of good practice which could be reproduced elsewhere. Please contact Ataxia UK (email research@ataxia.org.uk).

If you are interested in or considering involvement in research studies, please refer to the Ataxia UK website (www.ataxia.org.uk).

Appendix 1 – List of neurologists at Ataxia UK
Accredited Ataxia Centres of excellence and
other Centres of expertise

Adult neurologists

**Dr Paola Giunti and
Professor Nicholas Wood**

Ataxia UK Accredited Ataxia Centre
National Hospital for Neurology &
Neurosurgery
London WC1N 3BG

Dr Marios Hadjivassiliou

Ataxia UK Accredited Ataxia Centre
Royal Hallamshire Hospital
Sheffield S10 2JF

Professor Patrick Chinnery

Department of Neurology,
University of Newcastle
Newcastle upon Tyne NE2 4HH

Dr Rajith de Silva

Queen's Hospital, Romford
Essex RM7 OAG

Dr Nick Fletcher

The Walton Centre for Neurology and
Neurosurgery NHS Trust
Liverpool L9 7LJ

Dr Simon Hammans

St Richard's Hospital
Chichester
West Sussex PO19 6SE

Dr Neil Robertson

Department of Neurology
University Hospital Wales
Cardiff CF14 4XN

**Professor Anthony Schapira and
Dr Tom Warner**

Royal Free and University College
Medical School
London NW3 2PF

Dr Kevin Talbot

John Radcliffe Hospital
Oxford OX3 9DU

**Professor Patrick Morrison/
Dr Mark Gibson/
Dr Gavin McDonnell**

Belfast City Hospital Trust
Belfast BT9 7AB

Paediatric neurologist

Professor Robert Surtees

Great Ormond Street Hospital
London WC1N 3JH

Primary care

U&Es, Creatinine, liver enzymes, γ -GT, Ca, Phos, Igs, electrophoresis, TFT, Chol, FBC, ESR/CRP, Vit B12, Folate, CXR

Secondary care**1st line**

MRI of the brain, Vit E and lipoproteinemia, α -FP, Blood film, Lactate, Copper, Caeruloplasmin, 24hr-urinary copper, cervical spine, LP (cells, protein, glucose*, cytology, oligoclonal bands*, Lactate, Ferritin), syphilis

**with blood*

2nd line

Phytanic acid
 Peripheral nerve conduction studies
 Electromyography
 Electroencephalography
 Neuropsychology
 Ophthalmology
 Anti-gliadin abs (IgG and IgA)^a
 Anti-GAD
 Anti-VGCC
 Anti-Hu/Yo
 CT of chest, abdomen and pelvis
 Total body PET
 Muscle biopsy
 White cell enzyme
 Long chain fatty acids
 14-3-3 protein in CSF (prion conditions)^b
 Cholestanol
 Coenzyme Q10 (ubiquinone)^c

All the diagnostic tests in the panel on the left should be readily available in primary or secondary care. The following are only available in certain laboratories:

a) If testing for antigliadin antibodies is not readily available, clinicians can contact Dr Marios Hadjivassiliou who runs a specialised gluten ataxia clinic.

Contact details:

Royal Hallamshire Hospital, Sheffield S10 2JF.
 Tel: 0114 271 2502.

b) Testing for 14-3-3 protein in the CSF can be carried out at the National CJD Surveillance Unit, Western General Hospital, Edinburgh.

Contact Alison Green to discuss individual cases before sending samples for testing.

Tel: 0131 537 3075

email: alison.green@ed.ac.uk

c) Testing of Coenzyme Q10 levels for ataxia with Coenzyme Q10 deficiency can be performed on skeletal muscle samples or on blood mononuclear cells.²³

Testing is available at the Neurometabolic Unit, National Hospital for Neurology and Neurosurgery, London.

Contact Dr Ian Hargreaves or

Dr Simon Heales

ian.hargreaves@uclh.nhs.uk or

simon.heales@uclh.nhs.uk

Tel: 0845 155 5000 ext 723844

Genetic tests

(Underlined tests available 'routinely' via the UK genetics testing network)

The following genetic tests are also available from research laboratories. Details of neurologists to contact for arranging these tests are given.

Testing for AT, AOA1 and AOA2
Professor Malcolm Taylor, CR-UK Institute for Cancer Studies, University of Birmingham.
A.M.R.TAYLOR@bham.ac.uk

Genetic testing for episodic ataxia types 1 and 2
Dr Marina Frontali, Istituto di Neurobiologia e Medicina Molecolare, CNR, Frascati (RM), Italy
marina.frontali@artov.inmm.cnr.it

Testing for GSS syndrome (Gerstmann-Straussler-Scheinker syndrome) and other prion-related genetic disorders can be carried out at the National Prion Prion Clinic, London (www.nationalprionclinic.org). It is also provided by the National CJD Surveillance Unit, Edinburgh (www.cjd.ed.ac.uk).

For further details of other laboratories in European countries providing diagnostic tests go to www.orpha.net (ORPHA97)

Autosomal recessive

FRDA

AT

AOA

Vit E deficiency

Autosomal dominant

Type 1 SCA1, SCA2, SCA3
SCA12, SCA17, SCA13

Type 2 SCA7

Type 3 SCA6, SCA10, SCA14,
SCA5

EA type 1

EA type 2

DRPLA

GSS

Mitochondrial

NARP

'X-linked'

Fragile X

Appendix 4 The autosomal dominant spinocerebellar ataxias (SCAs)

SCA	Location	Gene	Mutation	Harding type	Clinical/other features
SCA1	6p23	Ataxin-1	CAG rpt	I	
SCA2	12q24.1	Ataxin-2	CAG rpt	I	Slow saccades
SCA3	14q32.1	Ataxin-3	CAG rpt	I	= Machado-Joseph
SCA5	11q13	B-III spectrin (SPTBN2)	In-frame deletion, missense	III	One kindred descended from President Lincoln's grandparents
SCA6	19p13	CACNA1A	CAG rpt	III	Allelic with EA2/FHM
SCA7	3p14-p21.1	Ataxin-7	CAG rpt	II	Retinal degeneration
SCA8	13q21	SCA8 gene	CTG rpt*		Not specific?
SCA10	22q13	Ataxin-10	ATTCT*	III	Seizures, Mexican
SCA12	5q31-q33	PPP2R2B	CAG rpt*	I	Tremor, Indian
SCA13	19q13	KCNC3	Missense	I	Mental retardation
SCA14	19q13.4-qter	PRKCG	Missense	III	
SCA17	6q27	TATA box-binding protein	CAG rpt	I	Psychiatric, dementia

*Mutation in non-coding (intronic) segment

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Disease references	Mode of inheritance	Gene location	Gene symbol (gene product)	MIM code
Hereditary ataxia/ movement disorder				
Spinocerebellar ataxia-1	AD	6p23	SCA-1 (ataxin-1)	164400
Spinocerebellar ataxia-2	AD	12q23	SCA-2 (ataxin-2)	183090
Spinocerebellar ataxia-3 (MJD) ^a	AD	14q32.1	SCA-3 (ataxin-3)	109150
Spinocerebellar ataxia-4 (puratrophin)	AD	16q22.1	SCA-4	600223
Spinocerebellar ataxia-5	AD	11p12-q12	SCA-5 (spectrin)	600224
Spinocerebellar ataxia-6	AD	19p13	SCA-6 CACNA1A	183086
Spinocerebellar ataxia-7	AD	3p12-13	SCA-7 (ataxin-7)	164500
Spinocerebellar ataxia-8	AD	3q21	SCA-8	603680
Spinocerebellar ataxia-10	AD	22q13	SCA-10 (ataxin-10)	603516
Spinocerebellar ataxia-11	AD	15q14-21.3	SCA-11	604432
Spinocerebellar ataxia-12	AD	5q31-33	SCA-12 PP2R2B	604326
Spinocerebellar ataxia-13	AD	19q13.3-4	SCA-13	605259
Spinocerebellar ataxia-14	AD	19q13.4	SCA-14 PRKCG	605361
Spinocerebellar ataxia-15	AD	3p24.2-pter	SCA-15	606658
Spinocerebellar ataxia-16	AD	8q23-24.1	SCA-16	606364
Spinocerebellar ataxia-17	AD	6q27	SCA-17 (TBP)	607136
Spinocerebellar ataxia-18	AD	7q31-32	SCA-18	607458
Spinocerebellar ataxia-19	AD	1p21-q21	SCA-19	607346
Spinocerebellar ataxia-20	AD	11	SCA-20	

Disease references	Mode of inheritance	Gene location	Gene symbol (gene product)	MIM code
Spinocerebellar ataxia-21	AD	7p15.1-21.3	SCA-21	607454
Spinocerebellar ataxia-22	AD	1p21-q23		SCA-22
Spinocerebellar ataxia-23	AD	20p13-12.3	SCA-23	
Spinocerebellar ataxia-24	AR	1p36	SCA-24 (SCASI)	607317
Spinocerebellar ataxia-25	AD	2p15-21	SCA-25	608703
Spinocerebellar ataxia-26	AD	19p13.3	SCA-26	609306
Spinocerebellar ataxia-27	AD	13q34	SCA-27	609307 (FGF14)
Spinocerebellar ataxia-28	AD	18p11-q11.2	SCA-28	
Spinocerebellar ataxia -**b	AD	—	SCA-	
Spinocerebellar ataxia, paraplegia, & mental retardation	AD	—	SPAR	607565
Ataxia with sensory/Motor Neuropathy	AD	7q22-32	SMNA	607458
Posterior column ataxia/retinitis pigmentosa	AR	1q31-32	AXPC1	609033
Infantile onset SCA	AR	10q24	IOSCA	271245
Friedreich ataxia	AR	9q13	FA (frataxin)	229300
Friedreich ataxia 2	AR	9p23	STM7/X25	601992
Charlevoix-Saguenay (Spastic ataxia)	AR	13q12	ARSACS (Sacsin)	270660
Hereditary spastic ataxia	AD	12p13	SAX1	108600
Vitamin E deficiency	AR	8q	AVED	277460
Congenital ataxia	AR	9q34-qter		213200
Childhood onset ataxia	AR	11p15	—	609270
Joubert Ataxia	AR	9q34.3	JBT1	213300
Congenital ataxia/neuropathy & Cerebellar atrophy	AR	9q33-34	AOA2 (SETX)	606002
Congenital ataxia/neuropathy	AR	14q31-2	SCAN1	607250
Abetalipoproteinaemia	AR	4q22-q24	ABL	200100
Ataxia-telangiectasia	AR	11q23	ATM	208900

Disease references	Mode of inheritance	Gene location	Gene symbol (gene product)	MIM code
Ataxia-telangiectasia like disorder	AR	11q21	hMRE11	604391
Ataxia-ocular motor Apraxia	AR	9p13	AOA1 (aprataxin)	208920
Cayman Island Ataxia	AR	19p13	ATCAY (Caytaxin)	601238 608179
Ataxia optic atrophy and deafness	AR	6p21-23		
Cerebellar ataxia, Developmental delay	AR	22q11		
Sensory neuropathy Dysarthria, ataxia (SANDO)	AR (Mito)	15q25	POLG	174763
Refsum disease 1	AR	10p11-pter	PHYH	600964
Refsum disease 2	AR	6q22-24,	PEX7	266500
Carbohydrate deficient glycoprotein syndrome 1a	AR	16p13	PMM2	601785
Tay-Sachs disease (GM2 gangliosidosis)	AR	15q23-24	HEXA	606869
Krabbe disease	AR	14q31	GALC	666890
Metachromatic leucodystrophy	AR	22q13	ARSA	607574
Wilson disease	AR	13q14-21	ATP7B	277900
Ataxia, neuronal migration defect	AR	16q13	BFPP	666854
Congenital Ataxia, deafness, and mental retardation	AR	—	—	—
Norwegian Ataxia	AR	20q11-13	CLA3	608029
Sideroblastic anaemia	XL	Xq13	ASAT	301310
Fragile X cerebellar ataxia	XL	Xq27.3	FMR1	309550
Coenzyme Q10 deficiency	Mito	Mito	CoQ10	607426
a. Machado Joseph disease.	b. Number not yet assigned.			

Further updates: In January 2007 the identification of a new recessively inherited pure cerebellar ataxia from a French-Canadian cohort was published. Mutations

in SYNE1 were found to be causative of this ataxia.³⁰ A useful review of the autosomal recessive cerebellar ataxias can be found in *Lancet Neurology* in 2007.³¹

Research studies on medical interventions for some symptoms experienced by patients with progressive ataxias are described in this section.

NB Unless otherwise stated, these studies of symptomatic treatments are not specific to ataxic patients.

Nystagmus

Nystagmus often causes decreased visual acuity, as well as sometimes causing oscillopsia (a disabling subjective sensation of movement of the visual world). The eye movements do not require treatment if patients are asymptomatic, however therapy is necessary when visual disability is present. There have been a few randomised controlled trials; these have shown the efficacy of gabapentin in treating symptomatic pendular or gaze evoked jerk nystagmus,^{32,33} and sometimes downbeat nystagmus too.³³ Downbeat nystagmus can also be treated with 3,4 diaminopyridine and baclofen.^{33,34} A number of other studies (non-randomised

controlled trials) have shown the efficacy of other medications such as clonazepam and valproate for pendular nystagmus and of 4-aminopyridine for downbeat nystagmus.³⁵ Botulinum toxin injections have also been reported to be beneficial in some patients, although there are limitations to this approach (discussed in a review in 2002).³⁶

Tremors

Several types of tremor are seen in patients with ataxia; cerebellar intention tremor is the most common and it is difficult to treat. Some medications may also make the ataxia worse.³⁷

Clonazepam³⁸ has been reported to improve kinetic-predominant tremor and carbamazepine to improve cerebellar tremor.³⁹ Essential tremor has been treated with propranolol,⁴⁰ primidone,⁴⁰ or topiramate.⁴¹

There may be a growing role for functional neurosurgery, including deep brain stimulation, in the management of these symptoms. Such studies on the ataxias are limited. In a study of a patient with SCA2

chronic thalamic stimulation was shown to improve severe resting and action tremor.⁴²

Ataxia

There are currently no proven medications that ameliorate ataxia. Small pilot trials have been performed that have shown some improvements, but no large randomised controlled trials have been carried out as yet.

Gabapentin was shown to improve ataxia in an open label trial on ten patients with cortical cerebellar atrophy.⁴³ Ataxia was measured using a number of items in the international ataxia cooperative rating scale (ie spread of feet, walking capacities, knee-tibia test, finger-to-nose test), and all showed improvement after a four week period. In addition gabapentin was also shown to be effective in two sporadic cases of olivopontocerebellar atrophy. In one of the cases, the ataxia was noticeably reduced; the other resulted in improvements in dysarthria and oscillopsia.⁴⁴

Ondansetron was tested in two small trials; one was a placebo controlled trial in four patients with ataxia due to brain injury, where ondansetron showed a trend towards improvement only in tests of lower extremity ataxia but did not show improvements in other tests for ataxia.⁴⁵ The other trial was a placebo-controlled trial of 45 patients with a cerebellar disorder and that showed no effect of oral ondansetron on global cerebellar dysfunction. However, when an analysis of subgroups of patients was carried out, oral ondansetron was found to have a mild effect on posture and coordination of lower limbs in

some subgroups of ataxic patients, but even showed deleterious effect for coordination in patients with cortical cerebellar atrophy.⁴⁶

The drug lamotrigine was tested in a single study of six patients with SCA3; this was found to improve gait balance on the basis of single leg standing test tandem gait index. The study also showed a reduction in mutant (but not wild-type ataxin-3 protein), which may explain the improvements in gait disturbance.⁴⁷ Another small trial in SCA3 tested the effect of tandospirone, and seven out of ten patients showed a reduction in their ataxia rating scale score.⁴⁸

Episodic ataxias

Acetazolamide is the standard treatment for episodic ataxia type 2. The potassium channel blocker 4-aminopyridine has also been shown to prevent attacks of ataxia in one trial of patients with episodic ataxia type 2.⁴⁹

There are also medications that can be used for the treatment of episodic ataxia type 1, although there is variation on the efficacy of different drugs between families. Case studies and other small studies suggest that medications such as acetazolamide, sulthiamine or phenytoin could be effective.⁵⁰

Dystonia

A number of treatment options for dystonia, including oral drugs, botulinum toxin injections, surgical techniques and physiotherapy are available. A comprehensive review of the treatment of dystonia has recently been published.⁵¹

Primary Speech Impairments

Speech problems are generally assigned to three major categories:⁵²

Articulatory inaccuracy:

imprecision of consonants, vowel distortions, irregular articulatory breakdown

Prosodic excess:

slow speech rate, excessive and equalised stress, phoneme prolongation

Phonatory-prosodic insufficiency:

harsh voice quality, monopitch, monoloudness.

Treatment focuses mainly on the prosodic difficulties. Problems with segmental articulation are difficult to address, as it is affected more by discoordination than reduced range of articulatory movement. In addition, articulatory breakdown is often irregular and no particular phoneme groups can be addressed in treatment.

In establishing appropriate treatment aims for prosody, it is important to identify which symptoms are due to the cerebellar pathology and which are secondary to other problems, such as poor posture affecting speech and breathing.

Prominent treatment targets should include:

- Adequate respiratory support
- Optimum voice quality without vocal misuse
- Optimum rate of speech for intelligibility and naturalness

- Strategic pause placement to aid respiratory support and intelligibility
- Awareness of and improved control over
 - stress production
 - pitch variation
 - loudness variation

In addition, an assessment of environmental factors affecting communication should be carried out. Measures known to maximise the exchange of information between patients and their conversational partners include:

- reducing background noise
- ensuring eye-contact and good lighting
- providing the listener with additional cues, such as highlighting topic change
- educating listeners about the nature of the patient's speech problem and how they might best be helped during communication

Treatment techniques for the above therapeutic aims are not distinct to ataxia and can be sourced from a range of publications on the treatment of dysarthria (such as Yorkston et al. 1998).⁵³

If the patient's speech production has deteriorated to the degree that verbal communication has become difficult, supplementation with or full use of alternative and augmentative communication (AAC) aids (pen and paper, alphabet board, in severe cases electronic tools such as the Lightwriter) can be considered.

There is evidence that early treatment helps to maintain functional communication in patients with degenerative disorders. It is therefore important to refer patients to SLT as early as possible, even when they are not yet showing signs of speech deterioration.

Secondary Problems

The above mentioned speech impairments can result in a number of secondary symptoms, particularly in pragmatic areas. Such problems are seen in many patients with speech difficulties and are not restricted to ataxia. They can include a general withdrawal from communication, characterised by a reduction in the amount and variety of contributions made to conversations. Turntaking behaviour is also frequently affected if the patient has difficulties initiating

speech. In addition, communication can be negatively affected by listener attitudes or inappropriate strategies to aid conversation, such as completing utterances for the patient. Such problems are best addressed jointly with the patient and carer(s).

One should also be aware that depression is known to affect cognitive and language performance and linguistic functioning should therefore be assessed if the patient presents with a background of clinical depression.

If language problems are present, either due to depression or general cognitive decline, treatment will generally focus on environmental issues such as carer education. This will include raising awareness about the types of problems experienced by the patient, eg whether they have problems following long and complex statements or difficulties finding the right word. Strategies can be proposed that aid communication, such as breaking information down into smaller chunks. Direct work with the patient would also generally focus on raising awareness of their own difficulties and how to deal with these, such as asking for clarification more often, or using circumlocution when experiencing word-finding problems.

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