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Review Article
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A Detailed Study on Spinocerebellar Ataxias

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Spinocerebellar ataxias are neurodegenerative disorders involving the cerebellum and its connections. There are more than 30 distinct subtypes, 16 of which are associated with an identified gene. The purpose of this review was to provide information for the patient and caretakers or families for better understanding of the disease so that they are in a better position to help cerebellar ataxia patients with many problems they faced.

INTRODUCTION:

Spinocerebellar ataxias (SCA) represents a large and complex group of heterogeneous autosomal dominant degenerative diseases characterized by progressive degeneration of the cerebellum and its afferent and efferent connections. Other nervous system structures are typically affected, including the basal ganglia, brainstem nuclei, pyramidal tracts, the posterior column and anterior horn of the spinal cord, and the peripheral nerves.

SCA are clinically characterized by the presence of cerebellar gait and limb ataxia (with dysmetria, dysdiadochokinesia, intention tremor, dysarthria, and nystagmus), which may be accompanied by extracerebellar signs, such as ophthalmoplegia, pyramidal signs, movement disorders (including parkinsonism, dystonia, myoclonus, and chorea), dementia, epilepsy, visual disorders (including pigmentary retinopathy), and peripheral neuropathy.

CLINICAL PRESENTATION:

These diseases can manifest mainly in adult life, but also in adolescence or childhood. Certain features differ between patients and may help in making a precise diagnosis.

The following features are common presenting or early manifestations:

• Progressive ataxia of gait (usually broad based)
• Progressive limb ataxia including tremor
• Progressive slurring dysarthria
• Nystagmus

Later on during the course of these diseases:

• Ophthalmoplegia
• Dysphagia
• Parkinsonian features

A minority of patients may encounter:

• Decrease in visual acuity
• Cognitive decline

CAUSE:

The hereditary ataxias are categorized by mode of inheritance and causative gene or chromosomal locus. The hereditary ataxias can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner.

- Many types of autosomal dominant cerebellar ataxias for which specific genetic information is available are now known. Synonyms for autosomal-dominant cerebellar ataxias (ADCA) used prior to the current understanding of the molecular genetics were Marie's ataxia, inherited olivopontocerebellar atrophy, cerebello-olivary atrophy, or the more generic term "spinocerebellar degeneration." (Spinocerebellar degeneration is a rare inherited neurological disorder of the central nervous system characterized by the slow degeneration of certain areas of the brain. There are three forms of spinocerebellar degeneration: Types 1, 2, 3. Symptoms begin during adulthood.)
- There are five typical autosomal-recessive disorders in which ataxia is a prominent feature: Friedreich ataxia, ataxia-telangiectasia, ataxia with vitamin E deficiency, ataxia with oculomotor apraxia (AOA), spastic ataxia. Disorder subdivisions: Friedreich's ataxia, Spinocerebellar ataxia, Ataxia telangiectasia, Vasomotor ataxia, Vestibulocerebellar, Ataxiadynamia, Ataxiophemia, Olivopontocerebellar atrophy, and Charcot-Marie-Tooth disease.
- There have been reported cases where a polyglutamine expansion may lengthen when passed down, which often can result in an earlier age-of-onset and a more severe disease

phenotype for individuals who inherit the disease allele. This falls under the category of genetic anticipation.

CEREBELLAR DEGENERATIONS OF UNKNOWN CAUSE

This syndrome has also been termed "idiopathic cerebellar ataxia" (ILOCA). Clinically this disease resembles the autosomal dominant cerebellar ataxias, but with no family history or detectable mutation. Extrapyramidal and autonomic features may be more prominent and may be improved by symptomatic treatment (although anti-parkinsonian drugs seldom help much). Course and prognosis varies markedly between patients. Some patients initially diagnosed with this type of ataxia may then be given a specific diagnosis. For example they may be told they have multiple system atrophy (with cerebellar symptoms), or may be diagnosed as having gluten ataxia (which may respond to a gluten-free diet).

TYPES AND PREVELENCE:

SCA have a prevalence ranging from 1 to 5 cases per 100,000 individuals and disease onset typically occurs between 30 and 50 years of age, although cases developing before the age of 20 and after the age of 60 have also been described. The most common genetic ataxias worldwide are the autosomal dominant cerebellar ataxias, and Friedreich's ataxia (autosomal recessive). The prevalence of the former is between 0.2 and 3.0 per 100,000 and so there might be 1800 cases in the UK. With a European prevalence of Friedreich's ataxia of 2 per 100,000, one would predict a total of 1200 patients in the UK. Thirty-two different types of SCA have been identified to date, and these are designated SCA1 to SCA36. Dentatorubral pallidoluysian atrophy (DRPLA) has also been included in this group of disorders. The particular gene responsible for each type of disease has been identified for SCA types 1-3, 5-8, 10-15, 17, 27, 31, and DRPLA. The remaining types (SCA 4, 18-23, 25, 26, 28-30, 32, 33-35, and 36) have been defined by linkage studies, as the associated genes and mutations have not yet been identified (2,3,4,6,9,10,11,12). Finally, it should be mentioned that SCA types 9 and 24 remain undefined, and these two types have been reserved for disorders yet to be described in the literature. Additionally, SCA16 appears to be identical to SCA15, and SCAs 29 and 15, as well as SCAs 22 and 19, may represent different allelic forms of the same gene. SCA3 is the most common form of the disease worldwide, whereas the prevalence of types 1, 2, 6, 7, and 8 is varied depending upon the ethnic background of the population.

SCA 1

Age of onset for SCA 1 is usually after 20 years of age, and the disease manifests itself as gait imbalance, with ataxia (more pronounced in gait than in the limbs), dysarthria, nystagmus, hyperactive deep reflexes and, sometimes, ophthalmoparesia. The most common abnormal eye movement in SCA 1 is a significant increase in the amplitude of saccadic movements, leading to hypermetria. It can occasionally be associated with slow saccadic eye movements, bulbar paralysis, dystonia, chorea and cognitive dysfunction

Pathological examinations show that the systems most affected are the cerebellum (through loss of Purkinje cells and cells in the dentate nucleus), pons, middle cerebellar peduncle and olives. The disease was mapped to chromosome 6 in fact, it was the first ataxia locus ever mapped – and the genetic mutation was defined as an unstable expansion of a repeated CAG sequence (generally between 41 and 81 repeats). The number of CAG repeats is related to the age at which signs and symptoms first appear as well as the duration of the disease. In some cases a correlation was found between the pattern of transmission (for example, paternal transmission) and a greater increase in the number of CAG repeats, as well as the phenomenon of anticipation. This form of SCA corresponds to the entity previously described by Schut and Haymaker in 1951 SCA 1 has been detected in 4 to 19% of cases in different series of patients with SCA. However, in some series published to date, it is the most common form of SCA found; in some regions of Italy and Japan, for example, it represents 50% of all cases.

SCA 2

SCA 2 is characterized by cerebellar ataxia accompanied by dysarthria, tremor, hypoactive deep reflexes/arreflexia of the upper and lower limbs (defining the presence of associated peripheral neuropathy), fasciculations of the face and limbs, and characteristic slow saccadic eye movements. The main clinical characteristic of SCA 2 is the presence of cerebellar ataxia, cerebellar atrophy, which can be observed in neuroimaging examinations, peripheral neuropathy and slow saccadic eye movements. Other clinical manifestations are dystonia, chorea, parkinsonism, myoclonia and dementia. The first description of SCA 2 was by Wadia and Swami, in India in 1971, and the disease was later the subject of considerable study by Orozco in Cuba (Holguín) in 1990 Salem et al., using molecular analysis, studied 42 Indian families with SCA and concluded that SCA 2 was the most common form. The authors also found evidence of a common founding mutation Basu et al., investigating a series of nine different ethnic populations in India, concluded that SCA 2 was the most common Velazquez-Perez studied 125 families with SCA in Cuba and concluded that SCA 2 (present in 120 families) was the most common form. There was a high prevalence of this form of the disease in the province of Holguin (70% of the patients), especially in the city of Baguanos (where there was an incidence of 129.2 cases per 100,000 inhabitants), representing one of the highest rates of SCA in the world. SCA 2 has also been described in other countries with varying frequency.

SCA 2 is characterized by cerebellar atrophy, with a loss of Purkinje and granular cells, olivary neurons, substantia nigra and cells in the anterior horn of the spinal cord. The SCA 2 locus has been mapped to chromosome 12 (12q24.13), and the genetic mutation responsible for the disease is a CAG trinucleotide expansion with between 34 and 59 repeats. However, late onset of SCA 2 with a 33 CAG repeat expansion, which is sufficient to cause the disease, has been reported SCA 2 is characterized by cerebellar ataxia with dysarthria, tremor, hyporeflexia/deep areflexia of the upper and lower limbs (defining the presence of associated peripheral neuropathy), fasciculations of the face and limbs, and characteristic slow saccadic eye movements. The main clinical characteristic of SCA 2 is its association with cerebellar ataxia (with cerebellar atrophy being observed in neuroimaging examinations), peripheral neuropathy and slow saccadic eye movements. Other clinical manifestations are dystonia, chorea, parkinsonism, myoclonia and dementia. Cognitive deficits have been described in patients with SCA 2 with a frequency of 5 to 19%. SCA 2 is characterized by cerebellar atrophy with a loss of Purkinje and granular cells, olivary neurons, substantia nigra and cells in the anterior horn of the spinal cord. SCA 2 locus has been mapped to chromosome 12 and the genetic mutation responsible for the disease is a CAG trinucleotide expansion with between 34 and 59 repeats.

SCA 6:

Clinically, this form of SCA is characterized by "pure" cerebellar ataxia, which can be accompanied by dysarthria, nystagmus, dysphagia and even loss of proprioception and dystonia. Many patients have intense episodes of vertigo before the onset of ataxia, while in others there are intermittent episodes of ataxia (corresponding to episodic ataxia type 2) in parallel with the signs and symptoms of slowly progressive cerebellar ataxia. Generally, SCA 6 evolves slowly and progressively, with the clinical picture first appearing around 50 years of age. Neuroimaging reveals cerebellar atrophy, and pathological examination shows a loss of Purkinje cells in the cerebellar cortex as well as gliosis of the inferior olivary complex. Ishikawa et al. described the presence of polyglutamine aggregates in both the nucleus and cytoplasm of Purkinje cells in patients with SCA 6.This SCA is characterized genetically by an expansion of a CAG repeat between 21 and 31 units long in the gene responsible for the voltage-dependent calcium channel known as alpha 1 (CACNA1A4), which was mapped to chromosome 19p13.13.SCA 6 accounts for between 10 and 30% of all SCAs and is the second most common form of SCA in some series (e.g., in Japan). However, in certain regions of Japan,

such as the district of Kinski, this type of SCA is the most common form. From the clinical point of view, it is particularly important to stress that the SCA 6 mutation is allelic with episodic or sporadic SCA type 2 and hemiplegic migraine

SCA 7:

This type of SCA presents with cerebellar ataxia and progressive visual deficit caused by retinal degeneration (macular dystrophy). It can also be accompanied by pyramidal signs, ophthalmoplegia, parkinsonism and slow saccadic movements in particular. The neuropathological features are olivopontocere bellar degeneration in association with loss of retinal ganglion cells and pigmentary macular dystrophy 3-6.The locus of SCA 7 was mapped to chromosome 3 (3p14.1) by David et al. in 1996. One of the families they studied came from the Crateús region, in Ceará, Brazil. The pathological alleles have between 36 and 306 CAG repeats. The mutant proteins, which is known as ataxin 7 and has an unknown function, is expressed in many tissues, including the central nervous system, and only causes selective neuron death in the brain. The clinical picture can emerge from early infancy to the end of the fifth decade and progresses much more quickly in cases involving early onset of the condition. Anticipation may be present in these families. Although a less-common form of SCA, this type is found in various countries and is considered the most common form in Sweden and Finland.

SCAs

VERY RARE TYPES

The SCA types defined as SCA 4, 5, 11, 13, 14, 15, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29 and 30 represent very rare forms and have been diagnosed in a small number of cases in different parts of the world, some of which were only reported in isolated families. The autosomal dominant form of cerebellar ataxia known as dentatorubral-pallidoluysian atrophy (DRPLA) is a disease with a highly variable phenotype; it was first described in the Japanese, among whom it was reported to have a high incidence, and has been described more recently in African Americans ("Haw River" Syndrome) and Europeans.

The disease presents with cerebellar ataxia in association with three different clinical forms: (1) myoclonus epilepsy with dementia; (2) choreoathetosis with dementia (simulating Huntington's disease); and (3) a clinical picture of psychosis, parkinsonism and pyramidal signs. The mutation found in DRPLA is located on chromosome 12 (12p13.31) and consists of an unstable CAG expansion with 49 to 79 repeats that codes for polyglutamine.

DIAGNOSIS AND INVESTIGATIONS:

Examination of not only the nervous system but a detailed systemic examination is essential. Careful history may make the diagnosis without further investigation, particularly if there is a clear mode of inheritance within the family. It may be relevant to exclude multiple sclerosis, posterior fossa tumours, alcoholic cerebellar ataxia or ataxia as a non-metastatic manifestation of malignancy. Ataxia may be caused by medication, particularly phenytoin. Vitamin E deficiency may cause a progressive ataxia and should always be excluded, even if there are no over gastrointestinal problems.

***Investigations may therefore include*:**

NEUROPHYSIOLOGY

EMG and nerve conduction studies will confirm or reveal evidence of an axonal neuropathy in many of the ataxias discussed above, including all the recessive ataxias, the leukodystrophies, vitamin E deficiency, and many of the dominant ataxias, particularly SCA1 and SCA2. In SCA2, the brunt of the neuropathy is borne by the upper limbs. A demyelinating neuropathy is usual in Refsum's disease. Conditions notable for the absence of a prominent neuropathy include SCA6 (in most cases), SCA7 and DRPLA. Chronic denervation on EMG similar to motor neuron disease is often found in juvenile or adult-onset hexosaminidase. A deficiency Patients with mitochondrial disorders may have myopathic EMGs and axonal neuropathy. Those with paraneoplastic cerebellar degeneration and anti-Hu antibodies may have a sensory neuronopathy. External anal

sphincter EMG and autonomic function tests may be useful in the diagnosis of multiple system atrophy, and the EEG helps in the diagnosis of both sporadic and familial prion disease.

NEUROIMAGING

Early neuroimaging can be particularly useful in deciding which of the many investigation should be considered. Structural abnormalities, e.g. Chiari malformations are easily visualized. Isolated cerebellar atrophy is a common finding, consistent with some of the genetic ataxias, both dominant such as SCA6, episodic ataxia type 2, SCA10 and SCA14, and recessive disorders such as ataxia telangiectasia and ataxia with oculomotor apraxia. Isolated cerebellar atrophy may also be encountered in Gerstmann–Straussler–Scheinker disease, coeliac disease and paraneoplastic cerebellar degeneration. Other brain regions, most commonly the brainstem and cerebral cortex, are atrophic in the more complicated SCAs, DRPLA and mitochondrial cytopathies. MRI in Friedreich's usually shows a normal cerebellum but an atrophic spinal cord.

OTHER SPECIAL TESTS

Taken together with the clinical features, the results of MRI and neurophysiology may help guide which further special investigations should be performed.

Blood tests

A raised serum alpha-fetoprotein is found in 90% of patients with ataxia telangiectasia, while serum immunoglobulins IgA and IgG (particularly IgG2) are reduced. Hypoalbuminaemia is present in approximately 85% of ataxia with oculomotor apraxia type 1, and cholestanol is raised in cerebrotendinous xanthomatosis. Gonadotrophins should be considered in selected cases, particularly where there is evidence of hypogonadism. Refsum's disease is easily diagnosed by measurement of serum phytanic acid,which is characteristically raised. End-organ vitamin E deficiency is common to abetalipoproteinaemia, ataxia with primary vitamin E deficiency, and vitamin E deficiency secondary to poor diet or malabsorption. The serum vitamin E is low or very low in all three conditions. Acanthocytes in the blood film, and absent, very low and low density lipoproteins are central to the diagnosis of abetalipoproteinaemia. The absence of a cardiomyopathy, or impaired glucose tolerance, distinguish ataxia with vitamin E deficiency from Friedreich's ataxia.

Antibody studies

Anti-gliadin and antiendomysial antibodies may be requested if gluten sensitivity is suspected although certain authors argue that the presence of IgG antigliadin antibodies alone is sufficient for the diagnosis of 'gluten ataxia' as a marker of host hypersensitivity, in the absence of overt small bowel damage. A number of different antibodies have been identified as markers of paraneoplastic cerebellar degeneration; the most common is anti-Yo, and is most commonly found in association with gynaecological malignancies. A number of other antibodies have now been identified including anti-Hu and anti voltage gated calcium channel in lung cancer, antim-GluR1 and anti-Tr in Hodgkin's lymphoma, and anti-Ri in breast cancer.

Cerebrospinal fluid

Examination of the cerebrospinal fluid (CSF) may give helpful clues in certain cases. Routine tests should include cytology and oligoclonal IgG bands. CSF lactate and pyruvate may be raised in mitochondrial cytopathies. CSF 14-3-3protein and neuron-specific enolase are not specific for prion disease but may be suggestive. In paraneoplastic cerebellar degeneration, the CSF may be normal or show a few excess white blood cells, a mildly increased protein concentration, an increased IgG concentration, and oligoclonal bands in 50% (Rees *et al*. 2001).

Tissue biopsy

There are particular clinical features of mitochondrial cytopathies that should encourage more invasive investigations such as muscle biopsy, but the diagnostic yield will be low in the absence of suggestive features.

Trichrome stain may reveal 'ragged red' muscle fibres, and immuno-stain for cytochrome oxidase (COX, complex IV) and succinic dehydrogenase (SDH) are the easiest tests to perform – an increase in the number of COX-negative fibres may be the sole abnormality. Further studies include respiratory chain enzyme assays using homogenized muscle tissue. If the index of suspicion is still high, and all these investigations are normal, functional mitochondrial studies with an electrode that measures oxygen consumption can be performed on fresh muscle samples to detect respiratory chain enzyme abnormalities. Other invasive tests include tonsillar biopsy for vCJD, and skin biopsy for fibroblast culture for Niemann Pick disease type C.

GENETIC TESTS:

1. **Autosomal dominant inheritance:**

Genetic tests for an expanded CAG trinucleotide repeat in spincerebellar ataxia genes SCA1, SCA2, SCA3, SCA6 and SCA7 are readily available in most centres. These can be requested separately, although it may be cheaper and easier to request all five than a series of individual tests. These five genes account for about half of all patients with a clear autosomal dominant family history. A further four genes, specifically SCA10, SCA12, SCA14 and SCA17, have been identified but, for various reasons, routine analysis is not yet easily available; these mutations are likely to be rare in the population at large, and should only be considered in certain ethnic groups or patients with specific clinical features. Controversy still surrounds the validity of SCA8 as a cause of ataxia (Schols *et al*. 2003). As yet, the genes that cause SCA4, SCA5, SCA11, SCA13, SCA15, SCA16 and SCA18–SCA22 have not been identified. These *loci* each refer to a disorder that has been identified in only one or at most two families. Analysis of the prion protein gene is now routinely available and may be indicated if there is a suspicion of familial prom disease.

2. **Autosomal recessive inheritance:**

Bearing in mind the expanded phenotype of Friedreich's ataxia, it is wise to have a low threshold for testing for the Friedreich's gene even in ataxic patients without the typical phenotype, unless a clear dominant mode of inheritance is apparent. The vast majority (98%) of Friedreich's chromosomes contain expanded GAA repeats (Pandolfo 2001). However, the remaining 2% have point mutations that affect the coding sequence of the gene. Thus, a patient may have one expanded copy and one normal length copy with a point mutation. All the genes for the recessive ataxias, apart from ataxia with oculomotor apraxia type 2, have been identified. However, as they are usually only available on a research basis, the diagnosis is often more easily made on the basis of clinical signs, along with the haematological and biochemical tests.

3. **Mitochondrial cytopathies:**

Analysis of mitochondrial DNA may be indicated in the context of appropriate clinical signs and/or matrilineal inheritance. Requests are usually for analysis of the three most common point mutations associated with MERRF (A3243G), MELAS (A8344G) and NARP (T8993G), although other mutations have been described that produce both the MELAS and MERRF phenotypes. All these mutations can usually be easily identified in leucocytes DNA from peripheral blood. Kearns–Sayre syndrome is most commonly due to deletions of varying sizes, detectable only in the patient's mitochondrial DNA and not in their relatives and offspring (Moraes *et al*. 1989). In addition, the deletion may only be detected in muscle mitochondrial DNA, necessitating muscle biopsy to make the diagnosis. Very occasionally, external ophthalmoplegia and ataxia may be inherited in an autosomal dominant or recessive fashion (Kaukonen *et al*. 2000).

4. **Autosomal dominant episodic ataxias:**

Episodic ataxia types 1 and 2 are both channel opathies, i.e. they are caused by point mutations in the human potassium channel gene KCNA1 (Browne et al. 1994) and the cerebral P/Q-type calcium channel alpha 1

subunit gene CACNL1A4 (Ophoff et al. 1996), respectively. It should be noted that EA2 and SCA6 are allelic disorders – SCA6 results from expansions in the CAG repeat at the C-terminal end of the CACNL1A4 gene (Jodice et al. 1997). Interestingly, some patients with SCA6 may present with discrete episodes of unsteadiness similar to those of EA2; conversely patients with EA2 may develop a progressive ataxia after initially displayed the typical episodic phenotype. Genetic testing is not routinely available for suspected EA1 or EA2, as sequencing the genes is labour intensive, and the diagnosis usually depends on the clinical history, examination and responsiveness to acetazolamide. Hence it is worth requesting analysis of the SCA6 expansion in cases of suspected episodic ataxia with the EA2 phenotype, although usually this will be normal.

5. **Sporadic ataxia:**
How common are the existing SCA mutations or the Friedreich's expansion in individuals where there is no family history, and where acquired causes of ataxia have been excluded? SCA6 has been the most common dominant mutation detected with between 6% and 13% of patients having an expanded allele but it is not clear whether any were true new mutations. Two studies each identified one *de novo* SCA2 expansion (Futamura *et al*. 1998; Schols *et al*. 2000). The frequency of the Friedreich's expansion among cases of adult-onset ataxia without a family history and without the typical Friedreich's phenotype was between 4 and 8% in three studies (Moseley *et al*. 1998; Schols *et al*. 2000; Abele *et al*. 2002). Overall, a genetic explanation for 'sporadic' ataxia was obtained in 4–22%. As discussed previously, the absence of a family history does not exclude a genetic diagnosis. Hence, I would advocate testing for recessive ataxias including Friedreich's and for the SCAs in all patients with sporadic ataxia if initial investigations for sporadic causes prove inconclusive. Would it change the management if a genetic diagnosis could be proven? A genetic diagnosis in a presumed sporadic case clearly transforms the management of the patient, from prognosis to genetic counselling. In addition, if patients are not informed that there is a possibility that they can transmit the disease to their offspring, then the potential consequences are self-evident.

IF ALL THE TESTS ARE NEGATIVE

Despite thorough investigation, some patients will remain without a diagnosis. If this is the case, reconsider the family history, is it relevant and is it correct? Do you have accurate information about the age at onset? Are there any new tests, either genetic or non-genetic, which may be relevant? For example, if the phenotype is consistent with ataxia with oculomotor apraxia, is it worth sending off the DNA for aprataxin gene analysis to a research laboratory abroad, which might be happy to do this free of charge? A very useful resource is Online Mendelian Inheritance in Man (OMIM) based at the US National Center for Biotechnology Information (www.ncbi.nlm.nih.gov/Omim). Here the phenotypes of thousands of conditions, common and uncommon, as well as the various mutations in the genes responsible are described, and you can search for disorders with the clinical features of your patient. You might then identify the laboratories and groups working on the specific disorder and get in touch with them to see if they can help. Bear in mind also that as genes for well-known conditions are identified, and genotype–phenotype correlations are made, the text-books are constantly being rewritten as to what is, and what is not, a feature of a given disorder. And also that as more genes are identified, and are available for routine analysis, it is likely that the proportion of cases which are unexplained will fall.

Age at onset

Perhaps the most important feature of the history is the age at symptom onset, although this can be difficult to determine if the disorder has been very slowly progressive. This information greatly simplifies the differential diagnosis, particularly when the cause is genetic, because the genetic causes can be helpfully divided into those starting in infancy, i.e. before the age of two years, and those with an early (< 25 years) or late (> 25 years) onset

(Table 1) (Harding 1993). In contrast, most sporadic and acquired causes of ataxia (Table 2) tend to present in adulthood, although childhood onset is possible. Clearly, genetic ataxias do not always present in one or other age group, so adult neurologists should not only consider those conditions presenting in adulthood, because the onset in a given patient may have occurred in childhood, occasionally even in infancy. Furthermore, a number of hereditary conditions which usually present in childhood may present in adulthood, namely Friedreich's ataxia and mitochondrial disease. Similarly, many of the inborn errors of metabolism including Wilson's disease, hexosaminidase. A deficiency, the leukodystrophies and neuronal ceroid lipofuscinosis have adult-onset forms (Lamont 2004).

Early onset ataxia

The group of conditions often referred to collectively as the 'recessive ataxias' should be considered first in this age group (Di Donato *et al*. 2001). Friedreich's ataxia is the most common recessive ataxia worldwide. The age at onset is typically between 8 and 15 years. However, the clinical spectrum has widened considerably since Friedreich's original description and the diagnostic criteria later proposed by Harding (1981a). In particular, onset even in the seventh decade has been documented. The other less common recessive ataxias that should be considered are compared. These disorders are most easily distinguished on the basis of the physical examination but there are differences in age at onset, and certain symptoms may suggest the diagnosis. A history of intermittent ataxia with discrete attacks triggered by stress or exercise, with onset in late childhood or early adulthood, suggests one of the dominant episodic ataxias (EA). The duration of the attacks is perhaps the most helpful. Finally in this age group, variant Creutzfeldt–Jakob disease (CJD) should be considered when cerebellar ataxia presents subacutely in combination with variable degrees of cognitive impairment and psychiatric symptoms.

Late onset ataxia

Ataxia starting over the age of 25 years has the broadest differential diagnosis, and most patients are presenting to the adult neurologist are in this group. Causes can be separated into genetic and non-genetic and a detailed family history is therefore essential. The most common hereditary ataxias in this age group are known collectively as the autosomal dominant cerebellar ataxias, and individually as spinocerebellar ataxia (SCA) type 1,2,3, etc. This is confusing because the pathology does not always extend to the spinal cord as is implied in the name. Far more commonly, dysfunction of other brain structures occurs. For a given SCA, the age at onset in individuals is highly variable, and is not particularly helpful in trying to determine the mutation. An abnormally expanded CAG repeat sequence in the coding region of the gene is responsible for the disease in SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17. Age at onset tends to fall the length of the expansion increases. Anticipation, that is the tendency for successive generations to develop the disease earlier, and often with increasing severity, is accounted for by intergenerational instability of these repeats, which is disease-specific and tends to be greater when the affected father transmits the disease. The effect may be so dramatic that children can become affected before the transmitting parent. Childhood onset has not been described in SCA6, whereas other SCAs, particularly SCA3 and SCA7, may present before adulthood. It is important to remember that no single clinical sign is specific to a given SCA, although certain features may be suggestive. An inverse correlation between age at onset and number of CAG repeats also occurs in two other conditions that may present with prominent ataxia in adulthood – Huntington's disease and dentato-rubro-pallido-luysian atrophy (DRPLA). Familial prion disease, such as Gerstmann–Straussler–Scheinker disease, also presents in adulthood. Other important hereditary conditions that may present with a late onset predominantly cerebellar syndrome include the cerebellar syndrome associated with autosomal recessive hypogonadotrophic hypogonadism (Holmes ataxia) and Wilson's Disease. Finally, acquired causes of late onset ataxia such as

multiple sclerosis, 'gluten' ataxia and vitamin E deficiency may present at any age. Sporadic CJD typically occurs from the age of 50–75. Paraneoplastic cerebellar degeneration usually begins in the sixth or seventh decade, reflecting the increasing frequency of cancer with age.

TREATMENT AND PROGNOSIS

There is no known cure for spinocerebellar ataxia, which is a progressive disease (it gets worse with time), although not all types cause equally severe disability. Treatments are generally limited to softening symptoms, not the disease itself. The condition can be irreversible. A person with this disease will usually end up needing to use a wheelchair, and eventually they may need assistance to perform daily tasks. The treatment of in-coordination or ataxia mostly involves the use of adaptive devices to allow the ataxia individual to maintain as much independence as possible. Such devices may include a cane, crutches, walker, or wheelchair for those with impaired gait; devices to assist with writing, feeding, and self cares if hand and arm coordination is impaired; and communication devices for those with impaired speech. Many patients with hereditary or idiopathic forms of ataxia have other symptoms in addition to the ataxia. Medications or other therapies might be appropriate for some of these symptoms, which could include tremor, stiffness, depression, spasticity, and sleep disorders, among others. Both onset of initial symptoms and duration of disease can be subject to variation. If the disease is caused by a polyglutamine trinucleotide repeat CAG expansion, a longer expansion may lead to an earlier onset and a more radical progression of clinical symptoms.

MANAGEMENT ISSUES

GENETICS

Expert assessment is required before ataxia is ascribed to genetic causes. Patients may require assessment by both a neurologist and a clinical geneticist. Inheritance has to be investigated both by pedigree analysis and by appropriate molecular genetic testing. Some patients with familial ataxia will not have an identifiable genetic defect and this may hinder genetic advice. By definition, patients with idiopathic late onset cerebellar ataxia have no affected relatives and will normally be given a low risk of passing on the disease to their children. However, even in the absence of family history someone can still be diagnosed as having an inherited

cerebellar ataxia, so genetic tests should still be offered. Relatives of patients with autosomal dominant cerebellar ataxia will have a risk of carrying the gene. This risk can be assessed by a clinical geneticist; in children of gene carriers this will be approximately 50%, depending on their age. In families with an identifiable mutation, both predictive and prenatal gene testing is technically straightforward, in a manner similar to Huntington's disease. The decision to undergo such testing is difficult and personal. Support in making such decisions is available from genetic counsellors. Testing may influence life assurance and job prospects. Knowledge of genetic status may be emotionally difficult as well as affecting relationships with others. At-risk relatives will normally be helped in coming to their own decision by the genetic clinic. Testing for adult ataxias is not normally offered to those under 18 years of age, and should be postponed if there is significant depression or other stress factors such as divorce or, bereavement. Asymptomatic or symptomatic gene carriers may consider prenatal testing during pregnancy, in order to abort an affected fetus. Ideally the gene carrier and his/her partner should be counselled in the genetic clinic prior to pregnancy to discuss technical aspects of prenatal testing and to come to a decision about proceeding with testing. If there is an identifiable mutation, testing may be achieved by chorionic villus sampling at the end of the first trimester, with the intention of a therapeutic termination of pregnancy should the fetus be carrying the gene. Whatever the result, this can be an emotionally traumatic experience and couples require sympathetic support. Not all at-risk relatives seek genetic advice but those that do often find the genetic burden easier to bear once the situation has been fully and openly explained. Attending a genetic or neurology clinic carries no obligation to be tested,

although most individuals find neurogenetic testing to be beneficial, whatever the result.

SPEECH AND SWALLOWING

Patients are often frustrated by dysarthria, which can lead those unfamiliar with them to conclude that they are under the influence of alcohol. Later in the disease dysarthria may cause communication difficulties. Expert speech therapy advice is important, and may lead to alternative communication strategies. Dysphagia becomes more common as the disease progresses. In advanced disease this can lead to weight loss or aspiration. The latter should be suspected if the patient swallows with difficulty, coughs after swallowing or has repeated chest infections. Patients often benefit from a swallowing assessment by a speech therapist and subsequent advice. In a minority of patients with advanced disease, palliation with
percutaneous endoscopic gastrostomy (PEG) may be appropriate.

COLD FEET

Peripheral cyanosis, oedema and cold feet are common problems, reflecting a decline in muscle activity. Passive movements and attempts to keep the feet warm are often only partially successful.

SPHINCTER DISTURBANCE

This is uncommon except in late onset cerebellar degenerations of unknown cause.

DEPRESSION

All patients with progressive neurological disorders are susceptible to depressive illness. Low mood responds to antidepressants in the normal way. Counselling and non-drug treatments may also be helpful.

THERAPISTS

Modern management is aided by regular review with a multidisciplinary team, which may include neurologists, rehabilitation physicians and therapists. Close cooperation between professionals and the patient, family and carers is important. Physiotherapy is often valuable, particularly to preserve mobility. Advising on walking aids is difficult since the patient's major requirement is stability. Some patients may find a stick helpful. When walking is difficult, use of a "rollator" frame may be helpful. Referral to a wheelchair clinic for specialist seating advice is important at the appropriate stage of the disease. The key role of a speech therapist has been described. Cerebellar ataxia patients benefit from regular assessments by an occupational therapist. Appropriate advice on home modifications and aids can help preserve independence as the disease advances.

REHABILITATION:

Physical therapists can assist patients in maintaining their level of independence through therapeutic exercise programmes. In general, physical therapy emphasises postural balance and gait training for ataxia patients. General conditioning such as range-of-motion exercises and muscle strengthening would also be included in therapeutic exercise programmes. Research showed that spinocerebellar ataxia 2 (SCA2) patients with a mild stage of the disease gained significant improvement in static balance and neurological indices after six months of a physical therapy exercise training program. Occupational therapists may assist patients with incoordination or ataxia issues through the use of adaptive devices. Such devices may include a cane, crutches, walker, or wheelchair for those with impaired gait. Other devices are available to assist with writing, feeding, and self care if hand and arm coordination are impaired. A randomised clinical trial revealed that an intensive rehabilitation program with physical and occupational therapies for patients with degenerative cerebellar diseases can significantly improve functional gains in ataxia, gait, and activities of daily living. Some level of improvement was shown to be maintained 24 weeks post-treatment. Speech language pathologists may use both behavioural intervention strategies as well as augmentative and alternative communication devices to help patients with impaired speech.

CONCLUSION

SCAs constitute a large group of neurodegenerative diseases with a high degree of genotypic and phenotypic heterogeneity, making assessment by the clinical neurologist

extremely difficult. To date, around 30 types of SCAs are known and 16 genes have been identified. Careful and meticulous clinical assessment of patients with spinocerebellar ataxias can be of significant help in choosing suitable molecular tests to ensure that the etiology is correctly defined.

Above all this, not only finding the cause of the diseases, finding the cure for the diseases is also a great challenge for the pharmacist and medical professor around the Globe.

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