Autosomal Dominant Cerebellar Ataxia

Most forms of cerebellar ataxia are acquired disorders but hereditary forms can be autosomal dominant or recessive; a few are X-linked. By and large the dominant forms are less severe than the recessive ones. A search for **autosomal dominant cerebellar ataxia (ADCA)** on the Online Mendelian Inheritance in Man (OMIM) database yields a very large number of results[1].

Mapping of genes has shown a vast array of conditions, the names of many beginning with spinal cerebellar ataxia (SCA), reflecting the genetic classification[2]. These disorders not only vary genetically but also clinically. They are characterised generally by a slow progression of ataxia of gait, stance and limbs and by dysarthria with or without oculomotor dysfunction due to cerebellar degeneration. The degenerative process can be limited to the cerebellum, or may also involve the retina, optic nerve, pontomedullary systems, basal ganglia, cerebral cortex, spinal tracts or peripheral nerves.

One classification of ADCA is as follows[4]:

- **ADCA type I** - e.g., SCA1 to SCA4, SCA8, SCA10, SCA12, SCA23, SCA27 and DRPLA (dentatorubral-pallidolysian atrophy).
- **ADCA type II** - e.g., SCA7; conditions in this group are associated with pigmentary maculopathies.
- **ADCA type III** - e.g., SCA5, SCA6, SCA11, SCA29, SCA30 and SCA31; conditions are usually pure cerebellar syndromes.

These disorders may show the phenomenon of anticipation with earlier onset and more severe disease in successive generations.

Pathogenesis

There have been interesting models for the molecular basis of various ADCAs which may ultimately lead to improved therapeutic measures[5, 6].

Epidemiology

Prevalence of ADCAs has been estimated as between 0.3 to 2 per 100,000[7]. It has been reported from many countries around the world with clusters of certain types in various parts of the world reaching a prevalence of 5-7 per 100,000 in some populations[6].

Presentation

Onset is usually between the ages of 30 and 50 years, although early onset in childhood and later onset after age 60 years have been reported.

As well as cerebellar features there may be dementia, seizures, impaired proprioception, movement disorders and polymyoclonus.

Symptoms

The following features are generally typical, although there is some variation between diseases:

- Developmental delay.
- Episodes of altered level of consciousness or recurrent neurological symptoms.
- Family history of similar symptoms in a close relative.
- Neurological or developmental regression.
- Multisystem involvement in addition to neurological disease.
- Presence of a particular neurological sign.

Signs

- Ataxia is the fundamental neurological sign. Ataxia is the inability to maintain normal posture and smoothness of movement. There is a broad-based gait, scanning dysarthria, explosive speech, intention tremor, dysdiadochokinesia, dysmetria and abnormalities of eye movements.
- There may be movement disorders.
- The picture ranges from pure cerebellar dysfunction to mixed patterns of involvement with extrapyramidal, brain-stem and cerebral cortical involvement.

Differential diagnosis

There are many other forms of cerebellar ataxia, both acquired and inherited. A relatively important one is sporadic Creutzfeldt-Jakob disease that can present with predominantly cerebellar signs[8]. In most cases of hereditary disease there will be a family history - but not always. SCA1, SCA2 and SCA3 are mentioned here in further detail as they are the most common:
Spinocerebellar ataxia type 1 (SCA1)
SCA1 is due to a mutation on the number 6 chromosome\[^9\]. Symptoms are variable depending on the length of the CAG repeat in the genetic code.

- Onset is commonly in the 2nd to 5th decade (mean age of 37 years in one cohort).
- Gait ataxia, dysarthria, dysmetria, nystagmus, muscle wasting and dystonia are seen in the late stages of the disease.
- There is gradual progression of disability, with death occurring 10-30 years after onset\[^10\].

Spinocerebellar ataxia type 2 (SCA2)
SCA2 is due to a mutation on the number 12 chromosome and it is also known as Wadia-Swami syndrome\[^11\].

- Onset is between 2 and 65 years.
- Ataxia, facial fasciculation, lid retraction, dementia and peripheral neuropathy. The prognosis varies considerably, even within families.

Spinocerebellar ataxia type 3 (SCA3)
SCA3 is also called Machado-Joseph disease and affects people of Portuguese-Azorean descent. The clinical picture is variable. It has been traced back over 100 years in a single family. It is due to a mutation on the number 14 chromosome\[^12,13\].

- Onset is after the fourth decade.
- Ataxia, pyramidal and extrapyramidal signs, amyotrophy, facial and lingual fasciculations, ophthalmoplegia and exophthalmos are found.
- A late feature may be autonomic dysfunction\[^14\].
- The disease is gradually progressive with death usually occurring from cachexia or pulmonary complications after 6-29 years\[^13\].

Investigations

- MRI scan may show atrophy of the cerebellum and brain stem and sometimes cerebral atrophy.
- Electroencephalography may show features of epilepsy.
- Electromyography may demonstrate continuous motor unit activity.
- Genetic testing may be possible. All these diseases represent an abnormality of metabolism due to a defect on a chromosome.
Management

- Physiotherapy can help the ataxia
- Anticonvulsants may be required. In some forms acetazolamide is useful.

Prognosis

Prognosis is highly variable between the different types but improvement is unlikely. Comparatively little is understood of the molecular processes involved in these diseases and so there is little chance of significant interventions to improve prognosis in the near future\(^8\). There may also be multiple pathways involved.

Prevention

Genetic testing enables identification of the causative gene in 50-80% of cases of ADCA\(^{15}\). Pre-symptomatic testing is available but not always wanted. It is usually requested for family planning purposes. SCA3 is similar to Huntington’s chorea in that the onset is fairly late in life, there is no effective treatment and screening may produce much anxiety. Most has been done in Portugal where the incidence of SCA3 is high. The psychological impact of testing does not seem high\(^{16}\).

Further reading & references

1. Autosomal Dominant Cerebellar Ataxia; Search for term Autosomal Dominant Cerebellar Ataxia on OMIM database, Online Mendelian Inheritance in Man (OMIM).
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