Episodic Ataxia

Episodic ataxias are a group of genetic conditions that affect the nervous system and in particular the balance centre (cerebellum) and cause problems with co-ordination which are intermittent [Episodic ataxia, NIH Genetics Home Reference, 2018]. They are characterized by unpredictable spells of incoordination, loss of balance, often associated with slowly progressive ataxia (loss of co-ordination and balance). [Episodic ataxia, NIH Genetics Home Reference, 2018].

Researchers have identified at least eight types of episodic ataxia, designated type 1 to 8. The types are distinguished by their different signs and symptoms, age of onset, length of attacks, and, when known, genetic cause [Episodic ataxia, NIH Genetics Home Reference, 2018]. Episodic ataxia type 1 and 2 (EA1 and EA2 respectively) are the best characterized genetically. Episodic ataxia type 2 is by far the commonest type in the UK and the most well-known, but the rarer forms have been identified in single families and either associated with mutations in known genes or linked to potential genetic loci [Ataxia UK Management of the ataxias: towards best clinical practice, 2016].

What are the symptoms?

People with episodic ataxia have recurrent episodes of ataxia. During these episodes, many people can experience loss of co-ordination, clumsiness, vertigo (a subjective feeling of the room spinning), nausea, vomiting, migraine-like headaches, double vision, slurred speech, ringing in the ears and sometimes jumpy vision (oscilopsia). Rarely epilepsy can be associated with some of the EA. Muscle weakness, and paralysis affecting one side of the body (hemiplegia) may also occur during attacks and is often linked to migrainous headache. Additionally, some affected individuals (particularly those with EA1) have a muscle abnormality called myokymia (twitching of muscles) during or between episodes. This abnormality can cause muscle cramping, stiffness, and continuous, fine muscle twitching. [Episodic ataxia, NIH Genetics Home Reference, 2018]. Myokymia can occur in the hands, fingers and sometimes face and the tongue and is frequently accentuated during attacks. Attacks can occur spontaneously or they can be triggered by rapid sudden movements, or if one is startled. Anxiety, and fatigue also increase the susceptibility to an attack. EA-1 is a non-progressive disorder, but over many years some people show slight permanent ataxia and tremor

EA2 is by far the commonest form of EA and one of the commonest genetic ataxias in the UK. In EA2 patients present with attacks of cerebellar dysfunction lasting hours to several days, and can be associated with other neurological features such as hemiplegic migraine, migraine with or without aura, all of which merit treatment in their own right. With time the ataxia becomes progressive. [Ataxia UK Management of the ataxias: towards best clinical practice, 2016]]. Patients with EA2 may have learning difficulties resulting in some intellectual disability later on in life.

What causes episodic ataxia?

Episodic ataxia can be caused by faulty genes that play important roles in the nervous system. EA-1 is caused by mutations in potassium channels that may lead to problems with transmitting nervous impulses. EA-2 is caused by mutations in calcium channels. Calcium channels are important for maintaining the correct amount of calcium in cells which is important in the functioning of the cerebellum [Handb Clin Neurol. 2018;155:205-215.]

Researchers believe that in EA, the altering of the transport of ions in the brain, causes certain neurons to become overexcited and disrupts normal communication between cells. Although changes in chemical signaling in the brain underlie the recurrent attacks seen in people with episodic ataxia, it is unclear how mutations in these genes cause the specific features of the disorder.

How is episodic ataxia inherited?

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases, an affected person inherits the mutation from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family. Children of affected individuals have a 50% chance of inheriting the condition. Prenatal testing is possible for pregnancies at increased risk for EA2 if the pathogenic variant has been identified in the family. However, the condition is compatible with normal life span sometimes with minimal disability.

When do symptoms start?

Episodes of ataxia and other symptoms can begin anytime from early childhood to adulthood. Some children may have learning difficulties during schooling years. Episodes can triggered by environmental factors such as emotional stress, caffeine, alcohol, certain medications, physical activity, and concurrent illness. [Ataxia UK Management of the ataxias: towards best clinical practice, 2016].

How is episodic ataxia diagnosed?

A neurologist is often the most helpful specialist in diagnosing episodic ataxia. A careful history with particular attention to the description of these episodes is very important. A thorough neurological examination can determine whether a person has any evidence of residual ataxia. Observing a typical attack, if possible (eg on a video recording done by family members) can be extremely helpful. Besides the neurological exam, the neurologist will evaluate family history, and undertake investigations such as brain imaging and possibly electromyography (EMG) findings (particularly in EA1).

Currently diagnostic genetic testing is available for EA1 and EA2 and for some of the less common EA.

How common is episodic ataxia?

Episodic ataxia is uncommon, affecting less than 1 in 100,000 people. Types 1 and 2 have been identified in more than one family, and Type 2 is by far the most common [Episodic ataxia Gene reviews, last updated 2015].

Management of episodic ataxia

As stress may trigger attacks, stress avoidance or management techniques (e.g. meditation can be helpful. Other trigger factors identified by the individual should be avoided. It is also important to see a neurologist, who will monitor the condition, on a regular basis [Ataxia UK Medical Guidelines, 2016].

Once a diagnosis is confirmed there are a number of drugs that can be tried to prevent attacks. Please note that the use of any medicines would always need to be discussed with the GP or the Neurologist. Not all people respond well to certain drugs and some people may be susceptible to side effects. If one drug is ineffective or causes side effects there are other drugs that can be tried.

In EA2, acetazolamide, a carbonic-anhydrase inhibitor, is usually used as a first line medication for the prevention or reduction in the frequency of attacks. It has been used effectively in clinical practice for many years, but because of the rarity of the condition there have been no randomized controlled trials, and its mechanism of action is unknown. The main side effect is the development of sensory disturbance (tingling) in feet and hands. Some patients can tolerate this and it can be dose dependent. Long-term use of acetazolamide can be associated with renal calculi, gastrointestinal symptoms and fatigue. A useful alterative medication is flunarizine. Like acetazolamide, this drug has not been the subject of randomised control trials but it can be effective in reducing the frequency of attacks. The potassium channel blocker 4-aminopyridine has also been reported to have beneficial effects in preventing these attacks but this drug is not licenced for use in EA and is expensive.

In EA1 frequent attacks may be controlled with acetazolamide although there is some variation on the efficacy between individuals. Case studies and other small studies suggest that the frequency and severity of attacks may be controlled by anti-epileptic medications such as carbamazepine, phenytoin or lamotrigine, but again there is variable response between individuals.

This information leaflet was written by Ataxia UK in collaboration with Professor M Hadjivassiliou, Director of the Sheffield Ataxia Centre (Ataxia UK accredited Ataxia Centre), Sheffield Teaching Hospital NHS Foundation Trust, September 2019.