Friedreich’s Ataxia

What is Friedreich’s Ataxia?
Friedreich’s ataxia is an inherited condition that causes progressive damage to the nervous system resulting in symptoms which include muscle weakness, loss of balance and coordination (ataxia), speech problems and heart disease.

Friedreich’s ataxia is the most common form of hereditary ataxia, affecting about 1 in every 29,000 people. Friedreich’s ataxia is also sometimes called Friedreich ataxia and abbreviated to FA or FRDA.

What are the symptoms?
Symptoms usually begin between the ages of 5 and 15 but can appear as early as 18 months or as late as 40 or 50 years of age. About a quarter of people have what is considered late-onset Friedreich’s ataxia with symptoms appearing after the age of 25. An earlier onset is usually associated with a more severe course, but it is important to keep in mind that there is a lot of variability from person to person in the severity and range of symptoms experienced.

The main symptoms include muscle weakness and, of course, ataxia which is a loss of balance and coordination. It doesn’t affect parts of the brain involved in thinking.

The first symptom is usually difficulty in walking which may be noticed as frequent tripping or an unsteady walk. Balance and coordination continue to decline over time, and muscles in the legs become weak and easily fatigued, making it increasingly difficult to walk. Someone with the "typical" form of Friedreich’s ataxia might begin using a wheelchair anytime between ten and 20 years after disease onset.

Several years later problems with speech and swallowing may start to appear. This is due to incoordination and weakness of the tongue and other facial muscles. Later in the disease, ataxia and weakness of the arms and hands can interfere with tasks like writing or manipulating buttons and zips. Muscle spasms (spasticity) are also a problem for some people with Friedreich’s ataxia.

Loss of sense of touch is characteristic of Friedreich’s ataxia but often it is only detectable when a doctor tests for it. In a small fraction of people, Friedreich’s ataxia leads to hearing loss or visual impairment.

Foot deformity is a common problem in Friedreich’s ataxia and about two-thirds of people with Friedreich’s ataxia develop curvature of the spine (scoliosis). If scoliosis is severe it can interfere with breathing and may require surgery.

About three quarters of people with Friedreich’s ataxia have heart problems but the severity varies widely. Some people’s heart problems are only detectible by testing at the clinic and require no
treatment whereas others have life threatening heart problems. Heart disease may cause symptoms such as chest pain, shortness of breath and heart palpitations.

About 10 percent of people with Friedreich’s ataxia have diabetes, and another 20 percent have a mild form of diabetes called glucose intolerance.

Friedreich’s ataxia can shorten life expectancy, and heart disease is the most common cause of death. However, some people with less severe Friedreich’s ataxia live into their sixties, seventies, or older.

**How is Friedreich’s Ataxia diagnosed?**

A diagnosis of Friedreich’s ataxia requires a careful clinical examination, which includes a medical history and a thorough physical examination. The neurologist is likely to pay particular attention to testing reflexes, including the knee-jerk reflex. Loss of reflexes is an early and almost universal feature of Friedreich’s ataxia. Other signs that will be looked for include balance difficulty, loss of proprioception (joint sensation) and signs of neurological problems.

Genetic testing, which requires a blood sample, now provides a conclusive diagnosis. Other tests that may aid in the diagnosis or management of the disorder include:

- electromyogram (EMG), which measures the electrical activity of muscle cells
- nerve conduction studies, which measure the speed with which nerves transmit impulses
- electrocardiogram (ECG), which gives a graphic presentation of the electrical activity or beat pattern of the heart
- echocardiogram, which records the position and motion of the heart muscle
- blood tests to check for elevated glucose levels and vitamin E levels (vitamin E deficiency can cause similar symptoms to Friedreich’s Ataxia)
- magnetic resonance imaging (MRI) or computed tomography (CT) scans, tests which provide brain and spinal cord images that are useful for ruling out other neurological conditions.

**What causes Friedreich’s ataxia and how is it inherited?**

Friedreich’s ataxia is caused by changes (sometimes called mutations) in the FXN gene which contains the instructions for making frataxin protein. Normally, the gene contains five to 30 repeats of a three-letter code but in people with Friedreich’s ataxia, the gene contains hundreds of these repeats. Large numbers of repeats tend to cause an earlier onset and faster progression of Friedreich’s ataxia, but the association isn’t strong enough to predict the course of Friedreich’s ataxia in individual cases.

The frataxin protein has an important role in energy production in the energy factories of the cell, which are called mitochondria. Iron is essential for energy production in the mitochondria and it is thought that frataxin acts as a storage vessel for iron and releases it only when it is needed. If frataxin is missing or defective, excess iron is left floating around which stresses and damages the mitochondria. This stress is known as oxidative stress - the build-up of harmful oxygen-based free radicals.
Frataxin also provides the iron needed for synthesis of several key enzymes in the mitochondria. Therefore, a deficiency of frataxin results in a deficiency of these enzymes, further reducing mitochondrial function.

Mitochondria act as an essential energy source for nearly all of the cells in our bodies, which probably explains why Friedreich’s ataxia affects many different parts of the body including the muscles, nervous system, pancreas and heart. It is also thought that these parts of the body may be particularly susceptible to damage by free radicals.

Friedreich’s ataxia is inherited in an autosomal recessive pattern, which means that in order for a child to be affected, they must inherit two abnormal copies of the FXN gene, one from each parent. The parents, who each have one abnormal copy of the FXN gene are known as ‘carriers’, do not have any symptoms of Friedreich’s ataxia and usually don’t know that they are carriers. If both parents are carriers, they have a 1 in 4 chance of having an affected child. About 1 in 85 people of Caucasian background is a carrier of the Friedreich’s ataxia gene change.

Soon after the diagnosis of Friedreich’s ataxia it is essential that genetic counselling is arranged. Genetic counselling provides information on the inheritance pattern, risks to other family members, and the ‘prognosis’ (likely outcome of the disorder). Genetic counsellors aim to help individuals, couples and families understand and adapt to the medical and psychological implications of the diagnosis of a genetic condition in their family. A genetic counsellor can also explain family planning options to reduce the risk of passing the condition on to future children. For more information on genetic counselling please see our genetics information page.

How can the symptoms be managed?
In 2014, 39 international expert clinicians published clinical management guidelines for Friedreich’s ataxia. These guidelines are available for download (see references at the end of this factsheet) but they are written in technical language so may require discussion with your doctor. The key points of these guidelines are:

- Regular assessment of ataxia and muscle weakness should take place, and may guide referral to appropriate specialists in a timely fashion
- Physical therapy may be useful to help with balance, flexibility, accuracy of limb movements, maintenance of strength and reduce fatigue
- Occupational therapy may identify risks for people with ataxia as well as help minimize difficulties in the performance of daily activities
- Strategies such as an appropriate exercise program, aquatic physical therapy and stretches may be implemented to prolong the ability to walk, maintain heart health and reduce the number of falls
- Certain drugs may be helpful to treat neuropathic (nerve) pain
- Care should be taken with anaesthesia when going for surgery
- Protective foot care is important
- Physiotherapy and, if necessary, drugs can help to control muscle spasms (spasticity)
- People with Friedreich’s ataxia sometimes suffer from restless leg syndrome that may require treatment
• Speech and language pathologist can assess and help with speech difficulties
• A comprehensive swallowing evaluation by a speech and language pathologist should be done on a regular basis
• Diet and lifestyle modification and/or drugs may be needed to treat bladder and bowel dysfunction
• Screening for vision and hearing impairment is recommended
• Regular heart monitoring is recommended and extra care of the heart should be taken if undergoing surgery
• The guidelines provide recommendations for the treatment of heart problems in Friedreich’s ataxia
• There is increased prevalence of obstructive sleep apnoea in people with Friedreich’s ataxia so regular monitoring should be done
• Curvature of the spine should be monitored and surgery offered at the appropriate time
• Blood glucose should be measured at least once a year to screen for diabetes, and treatment including diet, exercise and insulin therapy started early
• Extra monitoring is recommended during pregnancy for women with Friedreich’s ataxia
• Individuals with Friedreich’s ataxia may benefit from regular counselling to assist in adjusting to transitional events and possibly prevent the emergence of related depression.
• Suitability of seating and wheelchairs should be evaluated on an annual basis in adults and bi-annually in children.

What research is being done?
In recent years scientists have begun to understand the causes of Friedreich’s ataxia, and work has begun to develop treatments and test them in clinical trials.

Antioxidants

Combating the oxidative stress inside the cells of people with Friedreich’s ataxia with antioxidants is another major strategy being explored. The most studied antioxidants for Friedreich’s ataxia are coenzyme Q10 and a modified version of it called “idebenone” which is more readily absorbed into cells. Coenzyme Q10 has also been tested in combination with vitamin E. Clinical trial results have been mixed but it has been suggested that it may have modest benefits for the hearts of people with Friedreich’s ataxia. The evidence is not strong enough for any drug authorities around the world to authorise idebenone’s prescription for Friedreich’s ataxia. However, since coenzyme Q10, vitamin E and idebenone are available as supplements and have few side effects, many individuals with Friedreich’s ataxia continue to take them.

Retrotope Pharmaceuticals has developed a stabilised polyunsaturated fatty acid (PUFA) that may be able to protect cells from oxidative stress. Tests in the laboratory are promising and clinical trials are planned.

Australian researchers recently tested resveratrol is a naturally occurring antioxidant from plants. 24 people with Friedreich’s ataxia took part in the trial and there were promising improvements seen in those taking a high dose of resveratrol. Based on these results, further clinical trials are warranted.
Several other antioxidant drugs and drugs that improve cellular energy production in the mitochondria are currently being tested in clinical trial. These include:

- RTA 408 (Reata Pharmaceuticals)
- acetly-L-carnitine (a naturally occurring compound made in the body)
- EPI-743 (Edison Pharmaceuticals)
- SHP622 (formally VP20629 or OX1, Shire plc)

Several other drugs that aim to protect cells from oxidant damage are also being developed for Friedreich’s ataxia in the laboratory.

**Increasing levels of frataxin**

Drugs that aim to increase levels of frataxin protein made from the faulty FXN gene are being developed and tested, some of which are described below. It is thought that the genetic change that causes Friedreich’s ataxia results in the FXN gene being “turned off”. However, certain substances may be able to switch it on, resulting in the production of the much needed frataxin protein.

Horizon Pharma are testing a drug called ACTIMMUNE in clinical trial, which is similar to a protein made in the body called “interferon gamma”. This drug is currently prescribed for other conditions such as Chronic Granulomatous Disease. Interferon gamma has been shown to increase frataxin levels in both cell and animal models of Friedreich ataxia.

A class of drugs called histone deacetylase (HDAC) inhibitors are also thought to be promising candidates for switching on the faulty FXN gene. Researchers at Imperial College London are testing a HDAC inhibitor called “nicotinamide”. Drug company BioMarin and researchers at Scripps Research Institute in California are developing other HDAC inhibitors for Friedreich’s ataxia.

Researchers studying diabetes drugs called “incretin analogs” have unexpectedly found that they increase frataxin levels in the pancreases of people with Friedreich’s ataxia. This has led to the start of a small pilot trial in Belgium to see if these drugs have potential as a treatment for Friedreich’s ataxia.

Erythropoietin (EPO) is another substance that has been shown to increase frataxin levels in laboratory tests and in a small pilot study involving people with Friedreich’s ataxia. EPO is a hormone produced in our bodies and is also an approved drug used to increase numbers of red blood cells. There are question marks over the safety of this treatment so further trials are ongoing to assess the benefits and risks. Drugs similar to EPO that may be safer are also being developed.

**Frataxin replacement and gene therapy**

In the laboratory, researchers are working on developing frataxin protein replacement and gene therapies for Friedreich’s ataxia. This would involve delivering either synthetically made frataxin protein or a healthy copy of the FXN gene into the cells of the body. Companies involved in this research include Chondrial Therapeutics, BioBlast Pharma, Voyager Therapeutics, AAVLife and Agilis Biotherapeutics. Tests in the laboratory have been promising so it is hoped that this research may lead to clinical trials.
NOTE: Research is moving forward at a fast pace, so this research summary may not be up-to-date at the time of reading. Feel free to contact MDA’s Scientific Communications Officer for an update on the latest developments - kristina.elvidge@mda.org.au.

Further information

- More information about the drug discovery pipeline for Friedreich’s ataxia can be found on the Friedreich’s Ataxia Research Alliance website
- A list of clinical trials for Friedreich’s ataxia can be found on the clinicaltrials.gov website. Note that some of these studies are “observational” which means that no new drug or treatment is given
- Clinical trials – your questions answered
- For definitions of any terms that you are not familiar with please take a look at our glossary
- Details of Friedreich’s ataxia support organisations around Australia and NZ can be found on the Friedreich Ataxia Research Association Australasia website
- You can get regular updates by becoming a friend of the MDA Facebook page or follow our Scientific Communications Officer on Twitter (@kelvidge)

For further information on any of the areas discussed above, please contact MDA:

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Revised April 2015.

References


Bidichandani SI and Delatycki MB. Friedreich Ataxia. Gene Reviews (updated July 2014)
