

Periodic Paralyses

The ability we have to control and move the muscles in our body depends upon the passage of electrical signals along the nerves and into our muscles. The periodic paralyses are conditions in which the muscles which control body movements [known as skeletal muscles] have a disturbance in their normal ability to allow the passage of these electrical signals.

Common symptoms in periodic paralysis

Patients with periodic paralysis experience intermittent (periodic) attacks of muscle weakness (paralysis). The muscle weakness may be confined to a small group of muscles e.g. the forearm and hand muscles alone resulting in weakness of grip. Alternatively, the muscle weakness may be more generalised e.g. the muscles of the arms and legs. When the weakness is generalised the patient may be completely unable to move [paralysis]. Even in a severe generalised attack it is very rare for the breathing, speaking or swallowing muscles to be involved. In the great majority of patients with periodic paralysis the heart muscle is not involved. In an uncommon form of periodic paralysis called Andersen's syndrome disturbances of the heart rhythm may occur.

At the end of an attack in all forms of periodic paralysis the muscle strength returns. In some patients as the years go by they notice a degree of persistent muscle weakness between the attacks of paralysis. If this persistent muscle weakness develops it can slowly get worse. The duration of an attack of weakness varies from minutes to days depending upon the exact type of periodic paralysis.

Different types of periodic paralysis exist

In the past classification was based upon changes in the level of blood potassium (which is normally between 3.5 and 5.1 mmol per litre) during, and particularly at the onset of, the attack. The three types in this classification are:

Hypokalaemic periodic paralysis: In these attacks the blood potassium is low

Hyperkalaemic periodic paralysis: In these attacks the blood potassium is high

Normokalaemic periodic paralysis: In these attacks the blood potassium remains normal

In fact, it has recently been discovered that it is not the change in the blood potassium level that is the primary problem in periodic paralysis. The primary problem in all of these conditions is that the normal pores which exist in the walls of the muscle cells don't work properly. It does seem that changes in blood potassium levels can further hinder the function of these pores and that is why changes in blood potassium can be relevant. However, other factors separate from blood potassium can also worsen the function of the pores, so a change in blood potassium is not essential.

Faulty ion channels cause periodic paralysis

The technical name for these pores is ion channels, because they allow the passage of ions into and out of the muscle cells. Ions are best thought of as small salt particles. Common examples of ions include sodium, calcium and potassium. It is the highly regulated passage of these ions into and out of the muscle cells that allows muscles to conduct the electrical signals required for muscle contraction. It is because these ion channels do not open and close properly the muscle cannot conduct electricity in the normal way. Since muscle contractions depends on this electrical conduction patients experience weakness. The factors which can trigger attacks of weakness [described below] seem to worsen the function of channels that are already not working properly, and this tips the balance resulting in an attack of weakness.

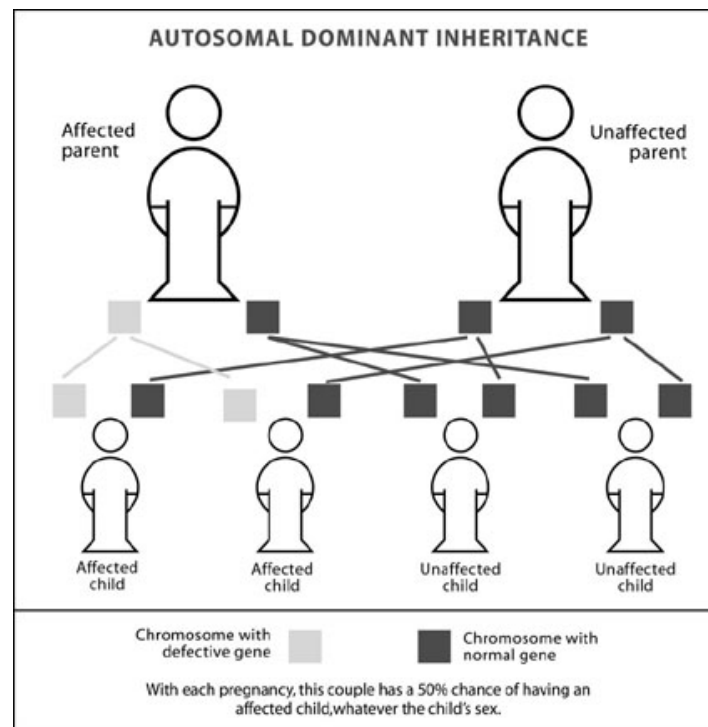
The blueprint for making each ion channel correctly is contained in our genes. There is a single gene for each of the three common channels i.e. the sodium channel, the calcium channel and the potassium channel. Changes in the genetic blueprint [know as gene mutations] result in the production of channels that don't work correctly and hence cause the conditions.

It is now possible to use a genetic classification of periodic paralysis that reflects the new genetic information. This is combined with the older classification based on potassium levels in the table below

	Channel affected	Gene responsible
Hyperkalaemic periodic paralysis: gene	Sodium channel	Sodium channel
Normokalaemic periodic paralysis gene	Sodium channel	Sodium channel
Hypokalaemic periodic paralysis gene	Calcium channel	Calcium channel
Andersen's syndrome channel gene	Potassium channel	Potassium

Inheritance

All the forms of periodic paralysis described are genetic. They are inherited in an autosomal dominant way (see figure) In practice this means that there is a 50:50 chance that a child of an affected person will also develop the condition.



Diagnosis and treatment of different forms of periodic paralysis

Hypokalaemic periodic paralysis

Hypokalaemic periodic paralysis is caused by genetic changes [mutations] in the calcium channel gene. It is the commonest form of periodic paralysis. The attacks usually start between the ages of 10 and 20 years, but may vary in frequency from several times a week to once a year. In some families the attacks are milder and less frequent in woman than in men. The attacks become less frequent in middle age, but by then some patients have a degree of permanent muscle weakness. Typically the attacks develop during sleep and weakness is present on waking. Gentle exercise may abort or shorten an attack.

Attacks may be provoked by:

- strenuous exercise
- carbohydrate-rich food
- salty food
- alcohol
- emotional stress

Diagnosis

This is not difficult in somebody with typical attacks and a positive family history. It is notable that one third of cases do not have any family history. If a blood sample can be taken during an attack, a low potassium level will help to confirm the diagnosis, but the change in potassium may be too slight to give a certain answer.

In the past if there was uncertainty about the diagnosis, the patient was admitted to hospital so that the doctors could try to provoke an attack, usually by giving glucose, either orally or by injection, and an injection of insulin. However, this is rarely needed these days because of the advances in genetics. It is now possible to analyse the calcium channel gene from a simple blood test. If a change [mutation] is found in the calcium channel gene this confirms the diagnosis and no further diagnostic tests are needed. Sometimes special electrical measurements of the muscles electromyography [EMG] are undertaken to provide further diagnostic information.

Occasionally, a muscle biopsy is required. This is a minor procedure in which the skin is numbed with a local anaesthetic and a small piece of muscle removed for examination under the microscope. The appearances may be normal in periodic paralysis, but during and shortly after an attack, and in patients with permanent weakness, little fluid filled cavities (vacuoles) may be seen in the muscle fibres

Treatment

Mild attacks may need no treatment and some patients find that light exercise can abort an attack. If they are more severe, potassium tablets (usually ones that can be dissolved in water) may shorten an attack, and if taken last thing at night may prevent the common problem of weakness on waking in the morning. It is important that potassium tablets are not dissolved in a drink that contains carbohydrate [such as a sweet drink] since large amounts of carbohydrate may bring on an attack.

If the attacks are very troublesome, acetazolamide tablets taken regularly can be very effective in preventing attacks. Acetazolamide is a diuretic (a drug which makes you pass more urine) and exactly how it works in hypokalaemic periodic paralysis is uncertain.

Hyperkalaemic periodic paralysis

The attacks are very similar to those described above for hypokalaemic periodic paralysis, but they tend to be shorter and occur during the day rather than on first waking. They also tend to start at a younger age, sometimes in early infancy. In virtually all cases there is a family history of attacks.

Attacks may be provoked by:

- cold
- fasting
- resting after exertion
- stress
- pregnancy
- alcohol

As with the hypokalaemic form, some patients eventually develop permanent weakness.

Some patients with hyperkalaemic periodic paralysis, but not those with hypokalaemic or normokalaemic periodic paralysis, also experience myotonia. This means that the muscles are unable to relax immediately after activity. Such stiffness is more marked in the cold. Patients may complain that their hands feel stiff, and the doctor may notice that when the patient looks upwards and then down, that the eye lids are slow to descend. There is a condition called paramyotonia congenita in which this cold-induced muscle stiffness is very pronounced; some of these patients also have periodic paralysis. It is now known that hyperkalaemic periodic paralysis and paramyotonia congenita are both due to the altered function of the sodium channel, but that the gene abnormality in each case is different.

Diagnosis

The diagnosis is relatively easy if there is a clear family history and the blood potassium level can be shown to be increased during an attack. If there is doubt, previously doctors may have tried to precipitate an attack, in hospital, by giving a potassium solution to drink. However, now it is usually possible to achieve a precise diagnosis by genetic analysis on a simple blood test. If genetic tests are inconclusive electrical tests (electromyography or EMG) may be helpful, particularly if they can be done during a spontaneous or induced attack. Muscle biopsy is occasionally helpful and the same comments as made for hypokalaemic periodic paralysis apply.

Treatment

Most attacks are brief and mild and don't require treatment. Eating or drinking carbohydrate-rich foods such as a sweet drink, bread or sugar cubes may shorten and reduce the severity of attacks. Fasting, unaccustomed exercise and exposure to cold should be avoided.

Very severe attacks, leading to hospital admission, may be treated by injection of glucose and insulin. If the potassium level in the blood is very high, calcium gluconate may also be given by injection, to protect the heart which can be affected by such high levels. Diuretic tablets make the patient pass more urine, which contains potassium, and can be very helpful if the attacks are frequent or severe.

If a patient is experiencing regular significant attacks they can usually be prevented or at least reduced by the drug acetazolamide described above. Another drug called salbutamol can also be a useful treatment for aborting acute attacks. This is a drug taken using a small inhaler device. It is most commonly used in asthma, but it has been shown that if a patient feels an attack of paralysis coming on, inhaling a small amount of salbutamol may stop the attack progressing.

Normokalaemic periodic paralysis

In some patients with periodic paralysis, the blood potassium level does not change during an attack. In other respects, the clinical features are very similar to those described above for the hypo- and hyper- kalaemic forms.

Attacks may be provoked by:

- physical activity
- cold
- alcohol

The frequency of attacks may be reduced by acetazolamide (see treatment of hypokalaemic periodic paralysis) and individual attacks may respond to salt tablets. There is now evidence that normokalaemic periodic paralysis is also caused by mutations in the sodium channel gene, the same gene that causes hyperkalaemic periodic paralysis.

Andersen's syndrome

Patients with Andersen's syndrome have attacks of periodic paralysis that may be hyper, hypo or normokalaemic. In addition, they have other clinical features which are not present in the forms of periodic paralysis described above. The most important additional feature is that the heart can also be affected. Patients may develop changes in the rhythm of the heart which can sometimes be significant and they may need close monitoring and treatment by a heart specialist [cardiologist]. A less important additional feature is that they may have mild changes in the appearance of their fingers and face.

The precipitants to attacks of paralysis are similar to those described above. Andersen's syndrome is caused by genetic mutations in a potassium channel gene.

Diagnosis

The diagnosis can be most easily achieved by genetic testing on a blood sample. A heart tracing [ECG] often shows typical changes in the heart rhythm such as extra beats.

Treatment

It is essential that all patients with Andersen's syndrome are assessed by a cardiologist. Specialised heart treatments may be needed if there are significant disturbances of the heart rhythm.

The attacks of paralysis can be effectively prevented by the drug acetazolamide.

Genetic Diagnosis in all forms of Periodic Paralysis

In the UK the Department of Health have funded a National clinical and genetic diagnostic service allowing any patient with suspected periodic paralysis in the UK to obtain a precise diagnosis. This is undertaken at the Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery, Queen Square, London. Further details can be obtained from Dr Michael G Hanna mhanna@ion.ucl.ac.uk

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