Hypokalemic periodic paralysis – an owner's manual

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This article focuses on questions that arise about diagnosis and treatment for people with hypokalemic periodic paralysis. We will focus on the familial form of hypokalemic periodic paralysis that is due to mutations in one of various genes for ion channels. We will only briefly mention other "secondary" forms such as those due to hormone abnormalities or due to kidney disorders that result in chronically low potassium levels in the blood. One can be the only one in a family known to have familial hypokalemic periodic paralysis if there has been a new mutation or if others in the family are not aware of their illness. For more general background about hypokalemic periodic paralysis, a variety of descriptions of the disease are available, aimed at physicians or patients.

Diagnosis

What tests are used to diagnose hypokalemic periodic paralysis?
The best tests to diagnose hypokalemic periodic paralysis are measuring the blood potassium level during an attack of paralysis and checking for known gene mutations. To exclude along-QT-syndrome and ventricular arrhythmias, Holter-ECG and Exercise ECG are indicated. Other tests sometimes used in diagnosing periodic paralysis patients are the late decrement of the Exercise EMG and the Compound Muscle Action Potential (CMAP) (i.e. long exercise test); further details are here. The CK is frequently increased by approximately the factor 2. Myotonic activity in the EMG favors the diagnosis of hyperkalemic periodic paralysis and speaks up against the hypokalemic form. Is molecular genetics unclear, can vacuoles and tubular aggregates in a muscle biopsy suggest periodic paralysis, although such changes are unspecific.

Although genetic analyses and whole-genome sequencing are widely used, the search for a causative genetic mutation can still be time consuming, expensive and inconclusive. Therefore imaging techniques can inform on the pathogenesis, potential therapy and prognosis. Muscle ultrasound and muscle 1H-MRI are reliable image techniques with high accuracy for the disease, which in most cases presents with a transient or permanent flaccid muscle weakness. The weakness can be caused by edemas, fatty muscle degeneration and muscle atrophy or a combination of these pathologies. The therapy is different for these processes. No treatment is currently available to stop or reverse the fatty degeneration, i.e. the replacement of muscle mass by fat and connective tissue.

However muscle edemas can be washed out by diuretics such as carbonic anhydrase inhibitors (acetazolamide, dichlorphenamide) and aldosterone antagonists such as spironolactone or eplerenone. These drugs lead to a repolarization of muscle fiber and an increase in their strength. A trial showed that dichlorphenamide reduces the frequency of hypokalemic weakness episodes. Dichlorphenamide (Keveyis© – Taro), an oral carbonic anhydrase inhibitor, has been approved for treatment of periodic paralyses and related variants. Dichlorphenamide is the first drug to be approved in the US for this indication. It was approved as Daranide in 1958 for treatment of glaucoma, but had not been marketed since 2002. Outside USA, it has the status of an orphan drug and can be therefore prescribed.

How can fatty degeneration muscle edemas and muscle atrophy be assessed?

The success of conventional and quantitative MRI is driven by advances in image acquisition, such as high-resolution and whole-body MRI acquisition. Because of better imaging hardware (e.g., improved coil technologies, homogeneous magnetic fields, and higher magnetic field strengths), the image quality and homogeneity improved significantly compared with early days of whole-body MRI applications in inherited

muscle diseases. Whole-body MRI assesses all muscles of the body and enable assessment of both fatty degeneration and muscle atrophy. but not edema.

Axial T1-weighted scans show lipomatous muscle degeneration. Short tau inversion recovery (STIR), also known as short T1 inversion recovery, is a fat suppression technique that assesses edema-like changes. Also edemas can be visualized by T2 mapping without (global T2) and with Fat suppression (water T2). Moreover edemas can be measured by an slowed ultrasound velocity or the Dixon technique. This method acquires two separate images with a modified spin echo pulse sequence. One is a conventional spin echo image with water and fat signals in-phase and the other is acquired with the readout gradient slightly shifted so that the water and fat signals are 180 degrees out-of-phase. The water-only image by the Dixon's technique can serve the purpose of fat suppression, an important and widely used imaging option for clinical MRI.

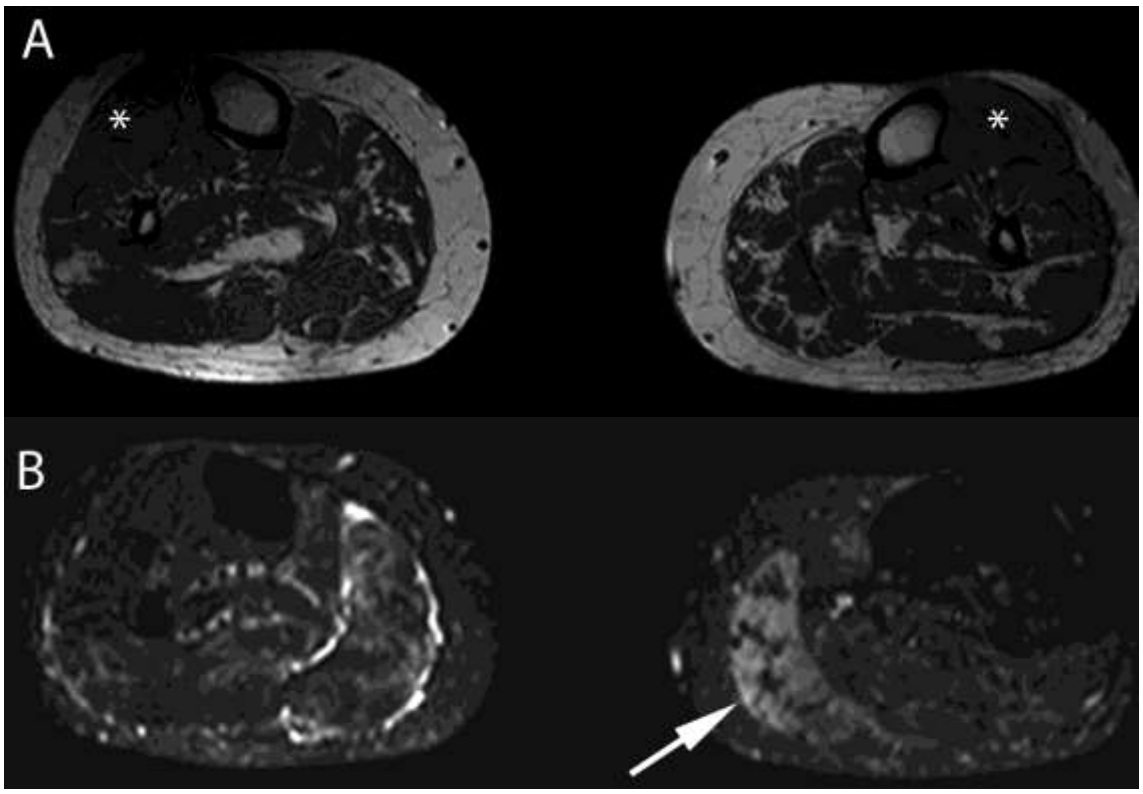

Fig. 1: MRI can distinguish between fatty degeneration and muscle edema. Cross sections of both calves of a 44-year-old woman with hypokalemic periodic paralysis (Mutation Cav1.1-R1239H) visualized by 3 Tesla MRT.

A: Axial T1-weighted scans show the fatty infiltration of the triceps surae muscles and the muscles of the deep posterior compartment (and the subcutaneous tissue). The tibialis anterior compartment is spared (asterisks). **B**: Short tau inversion recovery (STIR), also known as short T1 inversion recovery, is a fat suppression technique with an inversion time TI = ln(2)·T1fat, where the signal of fat is zero (black). STIR scans show edema-like changes in the medial head of the gastrocnemius muscle, which are pronounced on the left side (arrow). Modified after Jurkat-Rott and Weber, 2013.

The most definitive way to make the diagnosis is to identify one of the calcium channel gene mutations or sodium channel gene mutations known to cause the disease. However, known mutations are found in only 70% of people with hypokalemic periodic paralysis (60% have known calcium channel mutations and 10% have known sodium channel mutations). This situation will improve as further mutations are identified. In the meantime, if potassium helps relieve or prevent episodes, this fits with hypokalemic periodic paralysis.

If my blood potassium level is normal, does that prove I don't have hypokalemic periodic paralysis?

No. Although having low levels of blood potassium during attacks is typical of hypokalemic periodic paralysis, between attacks, people with hypokalemic periodic paralysis can have a normal blood potassium level (frequently in the low normal range).

Attacks of paralysis are typically triggered by the level of potassium dropping in the blood. Such potassium fluctuations occur in everyone, but in people with familial hypokalemic periodic paralysis, these drops in potassium can produce episodes of paralysis. For example, a large carbohydrate meal results in secretion of insulin into the blood, which results in a drop of the blood potassium level as potassium and glucose enter cells. In normal people, such a drop in blood potassium produces no symptoms. In people with familial hypokalemic periodic paralysis, however, the drop in blood potassium often triggers an episode of paralysis. Potassium levels in the blood can remain low as muscle is recovering from a recent attack. During an attack, muscles that become paralyzed swell and take up potassium, causing a drop in potassium in the blood. But as the swelling resolves, the level of potassium in the blood returns to the normal range. Consequently, a normal blood potassium after such a recovery should not be considered evidence against a person having hypokalemic periodic paralysis.

When evaluating blood potassium levels it is important to take into account recent treatments. Having just taken potassium or being on a drug that lowers blood potassium, such as acetazolamide, will have effects on blood potassium levels.

It is also important to consider other reasons for potassium being low. Some people have chronic low blood potassium, for example due to kidney disease (e.g., Bartter syndrome). They can have "secondary" or "symptomatic" periodic paralysis despite not having one of the familial "primary" periodic paralysis channel disorders.

How widespread is the paralysis?

Paralysis can affect all major muscles or can affect a single limb, for example after lots of exercise using that limb or after pain to the limb. Respiratory muscles can be involved, typically in a very severe attack or after anesthesia.

What is the inheritance pattern? What is the likelihood that people with a mutant gene will develop the condition?

Hypokalemic periodic paralysis is an autosomal dominant disorder, which means that one abnormal copy of the gene is all that is needed to have symptoms. Typically, this means that one parent has the disease, but it is possible to have the gene as a result of a new mutation not present in the parents, or it is possible that a parent has the gene but is not expressing symptoms enough to be clinically evident. Typically, someone will first show clear signs of hypokalemic periodic paralysis sometime in the teens, but with careful observation and knowledge of the paralysis triggers, the disease can be recognized earlier and in higher percentages of those carrying the gene abnormality.

What other diseases should be considered if one is considering a diagnosis of hypokalemic periodic paralysis?

Other diagnoses to consider are:
Normokalemic and hyperkalemic periodic paralysis (GeneReviews article here) and potassium-aggravated myotonia
Paramyotonia congenita
Andersen-Tawil syndrome (GeneReviews article here)
Thyrotoxic periodic paralysis
Autoimmune reactions to potassium channels
Diseases of oxidative metabolism such as mitochondrial diseases
Porphyria

Low potassium caused by foods and drugs: licorice, barium exposure, diuretics, steroids and others
Diseases in which potassium is chronically low because of kidney problems:
Renal Tubular Acidosis
Bartter syndromes and Gitelman hypomagnesemia-hypokalemia
Sjögren syndrome
Conn's syndrome (hyperaldosteronism)

What other symptoms can co-occur with hypokalemic periodic paralysis?

People with genetically-proven hypokalemic periodic paralysis often have other symptoms besides the paralysis:
Pain (by some reports pain is more commonly associated with sodium-triggered episodes)
Cramps

Among the 30% of people who appear to have hypokalemic periodic paralysis but don't have mutations in the two genes known to cause hypokalemic periodic paralysis the following are often noted:
Migraines
Heart rhythm abnormalities
Attention deficit disorder (ADD, ADHD)
Relative insensitivity to the local anesthetic lidocaine and "dental anxiety"
Severe premenstrual syndrome (PMS)

What other diagnoses are often given to people who have hypokalemic periodic paralysis?

"Conversion disorder" is a label often applied to people with hypokalemic periodic paralysis, mistakenly attributing symptoms to "hysterical" or "functional" paralysis. Such mistaken diagnoses have occurred after episodes of whole body paralysis or after episodes of single limb paralysis.

Is it worth having a muscle biopsy?

If you are thought to have hypokalemic periodic paralysis, a muscle biopsy can show some relatively non-specific changes such as vacuoles or tubular aggregates, which can support a diagnosis of hypokalemic periodic paralysis. However, such abnormalities are not specific enough to make a diagnosis definite. If your doctors are considering other possible disorders, for example mitochondrial disease, a muscle biopsy may be the key to making that diagnosis.

Prevention and Effect of Food and Drugs

What exposures trigger paralysis?

Foods:
Carbohydrates: The best known trigger of hypokalemic periodic paralysis is eating a large amount of carbohydrates. The most common circumstance is a meal of pasta, which typically contains a large amount of simple carbohydrates that are broken down to sugars and released quickly into the blood. Other common triggers are sugar-containing drinks and large amounts of candy. Once in the blood, the sugars trigger release of insulin, which causes cells to take up the sugars and also take up potassium from the blood. The lowering of potassium triggers the paralysis in hypokalemic periodic paralysis. Consuming less carbohydrates is helpful, but often hard to achieve. Another approach is switching to slower-release forms of carbohydrates such as whole wheat pasta or shredded wheat cereal that spread out the absorption of sugar and reduce the drop in potassium. Of note, attacks from sugar loading can occur nearly instantaneously or occur hours later (for example, the morning following a pasta dinner).
Salt: One of the most potent triggers of hypokalemic periodic paralysis is consumption of sodium chloride. The salt effect is far less known than the carbohydrate trigger, and many articles on hypokalemic periodic paralysis don't even mention this trigger. For many people it is easier to reduce salt than it is to reduce carbohydrates. Many foods contain huge amounts of salt, particularly snacks and tomato sauce. Restaurants

and movie theatres will often add large amounts of salt to many foods, most notably pizza, nachos and snacks such as popcorn. Soda drinks that contain both sodium and sugar are a particular problem.

Other:
Excitement / fear / epinephrine: Excitement or fear results in the body producing epinephrine, which makes episodes of paralysis more likely in some patients. Epinephrine injected to treat allergic reactions to foods, and epinephrine-like drugs such as albuterol used in asthma inhalers can trigger episodes of paralysis. This appears to be due to the effect of epinephrine in reducing blood potassium. The same pathway is often manipulated therapeutically: medications that block epinephrine effects such as beta-blockers are sometimes used to reduce the effect of epinephrine produced by the body. However, beta-blockers should be used only with caution, since they can produce severe problems in people with low blood pressure, slow heart rate (bradycardia) or asthma.
Exercise: After strenuous exercise there is increased risk of symptoms of hypokalemic periodic paralysis.
Cold environment: Muscles exposed to cold can become weak. Re-warming usually recovers muscle strength.
Anesthesia: During anesthesia there are many changes that can contribute to paralysis, including cooling, glucose, sodium and certain anesthetics such as succinylcholine. It is not clear that people with hypokalemic periodic paralysis are at any increased risk for malignant hyperthermia.
Alcohol: It is unclear why alcohol sometimes triggers periodic paralysis. It could be from electrolyte imbalance, dehydration, or increased exercise or dietary indiscretion that often accompanies the inebriated state.
Electromagnetic fields: There are reports that electromagnetic fields can trigger episodes of paralysis in a subgroup of people with hypokalemic periodic paralysis, but this has not yet been studied in detail.
What exposures trigger problems other than paralysis?
A subgroup of people with hypokalemic periodic paralysis appear to be particularly susceptible to heart rhythm abnormalities, especially when blood potassium is low but also at other times. Some people experience runs of slow heart rate (bradycardia) and fast heart rate (tachycardia), and many of these people are extremely sensitive to drugs that prolong the cardiac QT interval or drugs that increase heart rate.

What dietary interventions and medication will help me?

The most important interventions are managing the triggers described above. There are also a variety of drug interventions described in an article Practical aspects in the management of hypokalemic periodic paralysis by one of us who has hypokalemic periodic paralysis.
Dietary interventions are primarily a matter of avoiding triggers and increasing potassium. Implementation, however, is not simple. For example, bananas are widely known as a food high in potassium, but they also contain high levels of carbohydrates, so they are far from an ideal source of potassium. Other foods, such as shredded wheat cereal, which is typically high in potassium and contains slowly released carbohydrates, can be more helpful. Guidance from a nutritionist who understands hypokalemic periodic paralysis can be very helpful.

In individuals with hypokalemic periodic paralysis who have blood potassium values in the low normal range between attacks, it is difficult to keep blood potassium levels high enough to result in less muscle pain, less permanent weakness, and less frequent spells. So, in addition to aiming for potassium values in the normal to slightly high range, it is often helpful to use medications. A combination of acetazolamide, which slightly reduces blood potassium levels, and a potassium-sparing diuretic is preferred (typically triamterene, amiloride or aldosterone antagonists such as spironolactone or the newer agent eplerenone, which has less hormonal side effects compared to spironolactone). Sometimes, additional oral potassium intake is required. Individuals with hypokalemic periodic paralysis can become hyperkalemic and weak under this triple treatment. Therefore, potassium levels should be checked, typically weekly at the beginning, then monthly. Also, potassium should be checked when people are weak during a spell but do not recover within several hours.

Will I always eventually recover, even without treatment?

The body does tend to restore potassium levels, but during a severe episode there can be lasting effects on muscle. Many people with hypokalemic periodic paralysis develop chronic muscle weakness as they get older. In addition, some people are at risk of other effects such as heart rhythm disturbances or severe difficulty breathing, which can be life-threatening. That said, potassium almost uniformly restores muscle strength during an acute attack. With repeated attacks, and possibly simply with time, some people do experience an overall weakening of their muscles, especially of the thighs and shoulders.

What is involved with using the Cardy Potassium Meter to test potassium levels?

There is a detailed description here on the Periodic Paralysis International website. At present, this is not an U.S. FDA-approved device for checking potassium and is not endorsed by most leaders in the field as a reliable method for checking potassium to guide therapy. Some patients, at risk of false readings and non-standardized, non-validated protocols, have managed themselves successfully using this device.

Like an insulin pump – is there a potassium pump?

No. The rarity of the potassium-related diseases, the large amounts of potassium that would need to be given and the dangers of giving too much potassium make it unlikely that we will see "potassium pumps" used on patients other than for intravenous administration under medical supervision.

Can I reverse permanent muscle weakness with exercise? What type of exercise can I do when I feel very tired and weak? What should I tell my physical therapist and how do I help them understand that doing more exercise doesn't help? How do we identify a protocol for physical therapy to rebuild muscle or to strengthen weakened muscles?

Muscles have a large capability to grow with exercise, so even after some muscle damage it is possible to regain much strength. Some people have found that a program of regular exercise and muscle building is a way to keep paralysis at bay. However, following continued or severe attacks there can be some residual weakness and then exercise can do more harm than good.

Support and Precautions

What precautions and potential complications could occur with general anesthesia? Local anesthesia? What alternative anesthesia substances would be better for a patient with this condition?

With general anesthesia there is an increased risk of weakness and respiratory distress, so anesthesiologists must be told about a channelopathy diagnosis. Hypothermia, hypokalemia, sodium chloride and glucose infusions as well as myotoxic substances like succinylcholine in the operating room often lead to flaccid muscle weakness and respiratory distress in the recovery room. With local anesthetics the chief risk is from epinephrine added to local anesthetics to slow diffusion of the anesthetic away from the area. A separate issue is the insensitivity to the local anesthetic lidocaine seen in some people with hypokalemic periodic paralysis.

When should I start using a wheelchair? Should I start using a motorized wheel chair? Who will pay for my wheelchair? How can someone find out more about wheelchairs/scooters?

Permanent weakness occurs in about 50 % of people with hypokalemic periodic paralysis and slowly progresses with age. Over years the weak muscles can regain strength with proper treatment and precautions. If the majority of muscles is replaced by fat and connective tissue, current medication will not restore the muscles.

Few individuals will require a wheelchair. If a wheelchair is required it is best to choose one that is battery powered. Extended use of arms to propel a manual chair is discouraged. Patients should be aware that remaining physically mobile for as long as possible is desired. However, if the risk of falling becomes great, it is better to use a powered mobility device rather than to risk other bodily injuries in falls. During periodic paralysis attacks the use of a wheelchair can be useful to conserve strength during the recovery process. The Muscular Dystrophy Association will help patients with the purchase of both manual and motorized mobility devices. Many insurance carriers also cover these costs. If you have questions about this coverage you may contact the Periodic Paralysis Association (see resources).

How do I talk to my family members about this when they refuse to believe there is anything wrong?

The difficulty arises from the fact that the disease is rare, attacks can be infrequent and that there are variants of hypokalemic periodic paralysis with symptoms that tend to get dismissed as psychiatric.

For people with the standard form of hypokalemic periodic paralysis, convincing family members is primarily a matter of educating them about the existence of the disease. This can be done by making them aware of articles about the disease or by enlisting a physician who is aware of the disease to make clear that it is real, even though it is rare in the general population and the episodes of paralysis can be infrequent in an affected individual.

For people with the hypokalemic periodic paralysis variant with additional symptoms, the best that can be offered now is help avoiding episodes, and the prospect that the situation will improve as the relevant genes are identified.

Sometimes, speaking with others who have dealt with similar issues can help give you ideas about explaining others about your problem. To this end, various listservs are available (see Resources).

Resources:
Explanatory material for doctors: GeneReviews article
Explanatory material for patients and families: Do I have Periodic Paralysis?
Major centers of hypokalemic periodic paralysis expertise for diagnosis and genetic testing: For details contact Linda Feld of the Periodic Paralysis Association at the email address given on that site.
Patient support groups:
Periodic Paralysis Association and its listserv
Periodic Paralysis International and its resources

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