

## Hypokalaemic Periodic Paralysis

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Hypokalaemic periodic paralysis (HypoKPP) is an inherited disorder that causes occasional episodes of muscle weakness. It is one of a group of genetic disorders that also includes hyperkalaemic periodic paralysis and thyrotoxic periodic paralysis.<sup>1</sup>

The condition is caused by mutations in either of two genes. HypoKPP type 1, the most common form, is inherited as an autosomal dominant disorder with incomplete penetrance. These patients have mutations in the voltage-gated, skeletal muscle calcium channel gene, CACNAIS<sup>2</sup>. Approximately 10% cases are HypoKPP type 2, arising from mutations in the voltage-gated sodium channel gene, SCN4A.<sup>2,3</sup> An association with KCNE3 (voltage-gated potassium channel gene) has also been described, but is currently disputed.<sup>2</sup> Gene mutations, which cause the disorder, result in malfunction in certain ion channels in the skeletal muscle membrane. HypoKPP occurs in approximately 1 out of 100,000. The risk is slightly higher in Asian men who also have thyroid disorders.<sup>1</sup> The disorder causes attacks of muscle weakness or paralysis when the level of potassium in the blood drops (3.0 or lower). Most patients with HypoKPP have their first attack when they are 10 – 14 years old, but some patients don't have attacks until they are much older<sup>4</sup>. Men are more often affected because of decreased penetrance in women.<sup>3</sup> Patients who develop symptoms at a young age may only have an attack once in while to begin with, but attacks tends to come more often later, and may occur daily.<sup>4</sup> Episodic weakness with onset after age 25 years is almost never due to periodic paralysis with the exception of thyrotoxic periodic paralysis.<sup>3</sup>

Attacks may last an hour or two or some times a day or two. Attacks vary in severity from very mild weakness in a hand, foot or limbs in one time to complete paralysis in the next. Patients may also have abortive attacks - daily weakness which varies hour-to-hour or day-to-day. During severe attacks the patient may be unable to move and even appear unconscious. However even

during paralysis the patients are awake and completely aware of their surroundings.<sup>4</sup>

During an attack, muscles that become paralyzed swell and take up potassium, causing a drop in potassium in the blood<sup>5</sup>. When the level of potassium in the blood falls the malfunctioning ion channels fail to regulate the flow of ions properly. The ratio of sodium and potassium inside and outside the cell become unbalanced. This makes the muscle cell unable to contract properly<sup>4</sup>. If the imbalance becomes profound the muscle quits responding at all, i.e. is paralyzed. The persons with HypoKPP are very sensitive to drops in serum potassium. Some patients with this disorder may become paralyzed while their potassium levels remain within normal (frequently in the low normal range) limits.<sup>4</sup>

### *What triggers attacks of paralysis?*

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1. Eating a large carbohydrate meal
2. Consumption of excess sodium salt
3. Excitement/fear/sleep
4. Rest after unusual exercise
5. Cold environment, humid weather
6. Anaesthesia, alcohol, sleep, electromagnetic fields<sup>5</sup>
7. Medications e.g. muscle relaxants, beta-agonists, some tranquillizers, analgesics, antihistamines, some antibiotics, corticosteroids, insulin etc
8. Intercurrent illnesses like diarrhoea, upper respiratory infections, fever
9. Lack of sleep / fatigue and surgery.

### *Symptoms*

The disorder involves attacks of muscle weakness or loss of muscle movement (paralysis) that comes and goes. Initially, there is normal muscle strength between attacks. Some patients have attacks every day, while others have them once a year. Episodes of muscle weakness usually last an hour or two or (sometimes) a day or two<sup>1</sup>.

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*Location of the weakness or paralysis*

- Most commonly is located at the shoulders and hips. May also affect arms and legs.
- Ocular and bulbar muscles are less likely to be affected.<sup>3</sup>
- Respiratory muscles are usually spared but when they are involved, the condition may prove fatal.<sup>3</sup>
- A few patients have trouble in breathing and swallowing during severe episodes.
- Life-threatening cardiac arrhythmias related to hypokalaemia may occur during attacks.
- Attacks occur intermittently, most commonly occur on awakening after sleep or rest after unusual exercise<sup>1</sup>.

Other symptoms may include eyelid myotonia,<sup>1</sup> muscle pain, and cognitive problems during attacks. Migraines occur in up to 50% of patients. Less common symptoms like phantom smells, sensitivity to light and sound or loss of words may also occur.<sup>6</sup>

*Signs*

Between attacks, a physical examination shows nothing abnormal. Before an attack, there may be leg stiffness or heaviness in the legs. During an attack, muscle reflexes may be decreased or absent, and muscles go limp rather than staying stiff.<sup>7</sup> The low potassium level during attacks may cause irregular or weak heartbeats.<sup>4</sup>

*Other diagnoses to consider are<sup>5</sup>*

- Normokalaemic or Hyperkalaemic periodic paralysis
- Thyrotoxic periodic paralysis
- Paramyotonia congenita
- Renal tubular acidosis
- Conn's syndrome (Hyperaldosteronism),
- Porphyrin
- Low potassium caused by foods or drugs like diuretics, steroid, licorice etc.

Often misdiagnosed as having a conversion disorder or hysterical paralysis since the weakness is muscle based and doesn't correspond to nerve or spinal root distribution.<sup>5</sup>

*Tests used to diagnose HypoKPP*

- Serum potassium level: a low serum potassium level during an attack, excluding secondary causes, establishes the diagnosis.<sup>3</sup> There is no decrease in total body potassium, and blood potassium levels are normal in between attacks.<sup>7</sup>

- ECG: to detect or exclude any cardiac problem.
- Thyroid function tests: to rule out thyrotoxic periodic paralysis.
- Renal function and adrenal function tests: to rule out Hyperaldosteronism, renal tubular acidosis and diuretic abuse.<sup>8</sup>
- Exercise EMG,
- Compound muscle action potential (CMAP)<sup>5</sup>
- Genetic testing: Genetic testing has very high specificity but poor sensitivity. It is available on a research basis in various centers around the world.<sup>8</sup>

*Management*

The goals of treatment are relief of symptoms and prevention of further attacks.

During an attack potassium is given. Potassium chloride is the favored potassium salt. Liquid or aqueous forms of potassium are useful and the oral route is favored. Intravenous potassium should be avoided whenever possible, but it is indicated in arrhythmia due to hypokalaemia or airway compromise due to ictal dysphagia or accessory respiratory muscle paralysis. Mannitol (which is inert) should be used as the solvent rather than saline or dextrose, which are both potential triggers of attacks.<sup>9</sup> In cases where the patient has frequent early morning attacks, a sustained release potassium tablet taken at bedtime may be warranted.<sup>8</sup>

The total dose of potassium should not exceed 200 mEq in a 24-hour period for an acute attack. For intravenous administration, only 10 mEq of potassium per hour should be used at a time separated by anywhere from 20 – 60 minutes. When the attack resolves, potassium returns to the blood from the affected muscles. So, the idea is to administer just enough potassium to induce physiologic resolution of the attack.<sup>8</sup>

*Prevention of attacks*

Taking potassium supplements will not prevent attacks. For prevention of attacks a variety of diuretics are used. Diuretics are not helpful for acute attacks. Their role is to decrease the frequency and severity of attacks over time. The first line approach is acetazolamide 125 to 1000 mg per day in divided doses reduces or may abolish attacks in HypoKPP type 1. If attacks persist on acetazolamide, oral KCl should be added<sup>2,8</sup>. Dichlorphenamide a carbonic

anhydrase inhibitor may also be used. For peoples who don't respond to acetazolamide, potassium-sparing diuretics like a spironolactone, epleronone, triamterene, amiloride etc. may help. Epleronone is US FDA pregnancy category B and is the favored option for pregnant patients who cannot be managed on potassium supplementation alone. When one agent does not give adequate control, combination therapy of a carbonic anhydrase inhibitor and an aldosterone antagonist may be tried.<sup>8</sup> However, in patients with HypoKPP type 2, attacks of weakness can be exacerbated with acetazolamide.<sup>3</sup>

Identifying and avoiding triggers is imperative. Patients should be made aware of the importance of a low carbohydrate diet, low-sodium diet and consequences of intense exercise<sup>3</sup>. A common misconception is that one can increase banana intake to avoid paralysis. One would need to eat 6 bananas to get 72 mEq of potassium, which contains about 168 g carbohydrate<sup>10</sup>, a possible trigger of an attack of HypoKPP.

#### *Complications*<sup>7</sup>

- Kidney stones (a side effect of acetazolamide)
- Heart arrhythmias during attacks
- Difficulty in breathing, speaking, or swallowing during attacks (rare)
- Progressive muscle weakness, following repeated attacks.

#### *Outlook*

At present there is no cure of this disorder. A person who has HypoKPP will have the disorder lifelong, but treatment is available<sup>4</sup>. Most people with HypoKPP lead reasonably normal lives<sup>4,6</sup>. It responds well to treatment. Treatment may prevent, and even reverse progressive muscle weakness.

#### *Conclusion*

Hypokalaemic periodic paralysis cannot be prevented because it is often inherited, genetic counseling may be advised for couples at risk for the disorder. There are many questions regarding diagnosis and appropriate management of this condition still unanswered. Studies are needed to validate the diagnostic and management strategies that are currently in practice. It is hoped that with the combined efforts of various researchers and patient support organizations, a large enough cohort of genetically characterized

patients and families can be collected to answer these questions.

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