

## A CLINICAL REVIEW ON: HYPOKALEMIC PERIODIC PARALYSIS-DIAGNOSIS AND TREATMENT

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Article Received on 03/09/2017

Article Revised on 24/09/2017

Article Accepted on 15/10/2017

### ABSTRACT

Hypokalemic periodic paralysis is a rare, autosomal dominant channelopathy characterized by muscle weakness or paralysis with a matching fall in potassium levels in the blood (primarily due to defect in a voltage-gated calcium channel). In individuals with this mutation, attacks often begin in adolescence and most commonly occur on awakening or after sleep or rest following strenuous exercise (attacks during exercise are rare), high carbohydrate meals, meals with high sodium content, sudden changes in temperature, and even excitement, noise, flashing lights and induced by cold temperatures. Weakness may be mild and limited to certain muscle groups, or more severe full body paralysis. Attacks may last for a few hours or persist for several days. Recovery is usually sudden when it occurs, due to release of potassium from swollen muscles as they recover. Some patients may fall into an abortive attack or develop chronic muscle weakness later in life. Diagnosis can be achieved through a specialized form of electromyographic (EMG) testing called the long exercise test. This test measures the amplitude of a nerve response (called the Compound Muscle Action Potential or CMAP) for 40 to 50 minutes following a few minutes of exercise. Treatment of hypokalemic periodic paralysis focuses on preventing further attacks and relieving acute symptoms. Avoiding carbohydrate-rich meals, strenuous exercise and other identified triggers, and taking acetazolamide (Diamox) or another carbonic anhydrase inhibitor, may help prevent attacks of weakness. Some patients also take potassium-sparing diuretics such as spironolactone to help maintain potassium levels.

**KEYWORDS:** Autosomal Disease, Hypokalemic periodic paralysis, Mutation Spironolactone.

### INTRODUCTION

The heterogeneous group of muscle diseases known as periodic paralyses (PP) is characterized by episodes of flaccid muscle weakness occurring at irregular intervals. Most of the conditions are hereditary and are more episodic than periodic. They can be divided conveniently into primary and secondary disorders. General characteristics of primary PP include the following:

- (1) They are hereditary;
- (2) Most are associated with alteration in serum potassium levels;
- (3) Myotonia sometimes coexists; and
- (4) Both myotonia and PP result from defective ion channels.

Potassium is the most abundant intracellular cation and is necessary for maintaining a normal charge difference between intracellular and extracellular environments. Potassium homeostasis is integral to normal cellular function and is tightly regulated by specific ion-exchange

pumps, primarily by cellular, membrane-bound, sodium-potassium adenosine triphosphatase (ATPase) pumps.<sup>[1]</sup>

Hypokalemia is generally defined as a serum potassium level of less than 3.5 mEq/L in children, although exact values for reference ranges of serum potassium are age-dependent, and vary among laboratories. The alternative names are Periodic paralysis - hypokalemic; Familial hypokalemic periodic paralysis; HOKPP; HypoKPP; HypoPP. It is frequently present in paediatric patients who are critically ill and reflects a total body deficiency of potassium or, more commonly, reflects conditions that promote the shift of extracellular potassium into the intracellular space.<sup>[2]</sup>

Hypokalemic periodic paralysis is due to faulty genes. In most cases, it is passed down through families (inherited) as an autosomal dominant disorder. Occasionally, it occurs randomly in families, have very low blood levels of potassium and normal thyroid function during weakness episodes. Risk factors include a family history

of periodic paralysis. The condition occurs in approximately 1 in every 100,000 people.<sup>[3]</sup>

- In individuals with this mutation, attacks often begin in adolescence and most commonly occur on awakening or after sleep or rest following strenuous exercise (attacks during exercise are rare), high carbohydrate meals, meals with high sodium content, sudden changes in temperature, and even excitement, noise, flashing lights and induced by cold temperatures.
- Weakness may be mild and limited to certain muscle groups, or more severe full body paralysis. Attacks may last for a few hours or persist for several days.
- Recovery is usually sudden when it occurs, due to release of potassium from swollen muscles as they recover.

The two distinct forms of muscle involvement observed in hypokalemic periodic paralysis- they are:

*Paralytic episodes.* The primary symptom consists of attacks of reversible flaccid paralysis with a concomitant hypokalemia that usually leads to paraparesis or tetraparesis but spares the respiratory muscles.

*Myopathic form.* The myopathic form results in slowly progressive, fixed muscle weakness that begins as exercise intolerance predominantly of the lower limbs; it usually does not lead to severe disability. This fixed weakness must be distinguished from the reversible weakness that exists between attacks in some affected individuals.<sup>[4]</sup>

### Pathophysiology

Hypokalemia may be due to a total body deficiency of potassium, which may result from prolonged inadequate intake or excessive losses (including but not limited to, long-term diuretic or laxative use, and chronic diarrhea, hypomagnesemia, or hyperhidrosis). Acute causes of potassium depletion include diabetic ketoacidosis,<sup>[5]</sup> severe GI losses due to vomiting and diarrhoea, dialysis, and diuretic therapy.

Hypokalemia may also be the manifestation of large potassium shifts from the extracellular to intracellular space, as seen with alkalosis, insulin, catecholamines (including albuterol and other commonly-used beta2-adrenergic agonists), sympathomimetics, and hypothermia.

Other recognizable causes include renal tubular disorders, such as distal renal tubular acidosis, Bartter syndrome,<sup>[6]</sup> and Gitelman syndrome, periodic hypokalemic paralysis, hyperthyroidism, and hyperaldosteronism.

Other mineralocorticoid excess states that may cause hypokalemia include cystic fibrosis (with hyperaldosteronism from severe chloride and volume depletion), Cushing syndrome, and exogenous steroid administration. Excessive natural licorice consumption

can also cause or exacerbate potassium loss due to inhibition of 11-beta-hydroxysteroid dehydrogenase, which leads to elevated endogenous mineralocorticoid activity.<sup>[7]</sup>

### Symptoms

Symptoms include attacks of muscle weakness or loss of muscle movement (paralysis) that come and go. There is normal muscle strength between attacks.

Attacks usually begin in the teen years, but they can occur before age 10. How often the attacks occur varies. Some people have attacks every day. Others have them once a year. During attacks the person remains alert.

The weakness or paralysis:

- Most commonly occurs at the shoulders and hips
- May also affect the arms, legs, muscles of the eyes, and muscles that help with breathing and swallowing
- Occurs off and on
- Most commonly occurs on awakening or after sleep or rest
- Is rare during exercise, but may be triggered by resting after exercise
- May be triggered by high-carbohydrate, high-salt meals or drinking alcohol
- Usually lasts 3 to 24 hours.<sup>[8]</sup>

Other symptoms may include:

- Eyelid myotonia (a condition in which after opening and closing the eyes, they cannot be opened for a short time)

### Epidemiology

Hypokalemic periodic paralysis (PP) is the most common of the periodic paralyses, but is still quite rare, with an estimated prevalence of 1 in 100,000.<sup>[9]</sup> Hypokalemic PP may be familial with autosomal dominant inheritance or may be acquired in patients with thyrotoxicosis.<sup>[7-9]</sup> (See "Thyrotoxic periodic paralysis".)

Clinical penetrance is often incomplete, especially in women.<sup>[10]</sup> The disorder is three to four times more commonly clinically expressed in men. Approximately one-third of cases represent new mutations.<sup>[11]</sup>

### Mortality/Morbidity

With adequate control of potassium levels and resolution of any predisposing condition, the prognosis is excellent.

### Morbidity/mortality

Mortality is rare, except when hypokalemia is severe or occurs following cardiac surgery, when accompanied by arrhythmia, or in patients who have underlying heart disease and require digoxin therapy.

Short-term morbidity is common and may include GI hypomotility or ileus; cardiac dysrhythmia; QT prolongation; appearance of U waves that may mimic

atrial flutter, T-wave flattening, or ST-segment depression; and muscle weakness or cramping.

Mortality and morbidity can also be related to treatment for hypokalemia with potassium supplementation, particularly if potassium is given in large doses or rapidly. Because of the risk associated with potassium replacement, alleviation of the cause of hypokalemia may be preferable to treatment, especially if hypokalemia is mild, asymptomatic, or transient and is likely to resolve without treatment.<sup>[12-15]</sup>

### Complications

Complications of hypokalemia include the following:

- Hyperkalemia due to excessive/rapid potassium replacement
- Cardiac dysrhythmia (Irregular heartbeat during attacks)
- Gastric erosions
- Strictures
- Kidney stones (a side effect of acetazolamide)
- Difficulty in breathing, speaking, or swallowing during attacks (rare)
- Muscle weakness that worsens over time.

**Race:** Racial differences may be present in predisposing conditions such as Bartter syndrome, Gitelman syndrome, Conn syndrome (ie, hyper aldosteronism), Cushing syndrome, and familial hypokalemic paralysis. In addition, significant hypokalemia and hypokalemic paralysis develop in 2-8% of Asians with hyperthyroidism.<sup>[16]</sup>

**Sex:** No known sex predilection has been noted. **Age:** Viral GI infections tend to be more common in infants and younger children. Younger children with emesis or diarrhea are at an increased risk of hypokalemia because the depletion of fluid volume and electrolytes from GI loss is relatively higher than that found in older children and adults. Insulin-dependent diabetes mellitus that results in diabetic ketoacidosis (with its inherent fluid and potassium loss) is more common in children. Excessive corticosteroid and mineralo corticoid secretion, as in Cushing syndrome and Conn syndrome, is a less common cause of hypokalemia in the pediatric patient. Periodic hypokalemic paralysis may appear in childhood or young adulthood, precipitated by rest after strenuous exercise, physical or metabolic stress (eg, exposure to cold, alcohol ingestion), a high-carbohydrate meal, or exposure to exogenous insulin or catecholamines (eg, epinephrine and albuterol). Hypokalemia due to hyperthyroidism is generally observed in adults.<sup>[17]</sup> **Clinical Features:** The disorder involves attacks of muscle weakness or loss of muscle movement (Paralysis) that come and go. Attacks usually begin in childhood or in adolescence. How often the attacks occur varies. Some people have several attacks a day.

- Attacks typically last only 1 to 2 hours, but can sometimes last as long as a day. They are usually not severe enough to need therapy. Some people have associated myotonia, in which they cannot immediately relax their muscles after use.

The weakness or paralysis:

- Most commonly occurs at the shoulders and hips
- May also involve muscles of the eyes and those that help you breathe and swallow
- Most commonly occurs while resting after activity
- May occur on awakening
- Usually lasts 3 - 12 hours.

Situations that increase the risk of developing an attack.

**Carbohydrates:** The best known trigger of hypokalemic periodic paralysis is eating a large amount of carbohydrates. 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.

**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.

**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.

**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.

**Anaesthesia:** During anaesthesia there are many changes that can contribute to paralysis, including cooling, glucose, sodium and certain anaesthetics such as succinylcholine.

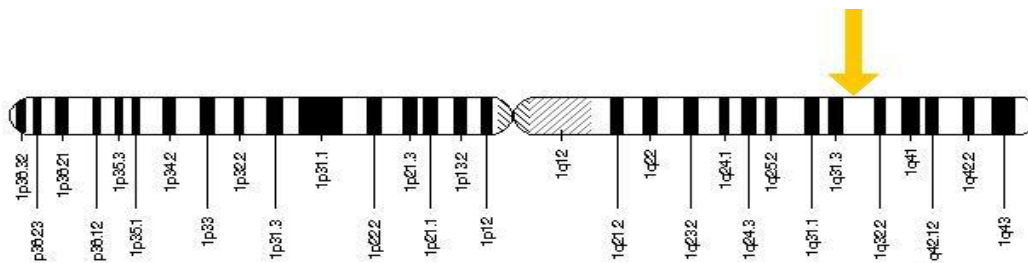
**Alcohol:** It could be from electrolyte imbalance, dehydration, or increased exercise or dietary indiscretion that often accompanies the inebriated state.

**Genetics:** Mutations in the following genes can cause hypokalemic periodic paralysis.<sup>[18-23]</sup>

## Types

Table 1: Mutations in the following genes can cause hypokalemic periodic paralysis.

Type	OMIM	Gene	Locus
HOKPP1	170400	<i>CACNA1S</i> (a voltage-gated calcium channel $Ca_v1.1$ found in the transverse tubules of skeletal muscle cells)	1q32
HOKPP2	613345	<i>SCN4A</i> (a voltage-gated sodium channel $Na_v1.4$ found at the neuromuscular junction)	17q23.1-q25.3

Figure 1: A voltage-gated calcium channel  $Ca_v1.1$  found in the transverse tubules of skeletal muscle cells. Locus: 1q32.

An association with *KCNE3* (voltage-gated potassium channel) has also been described.

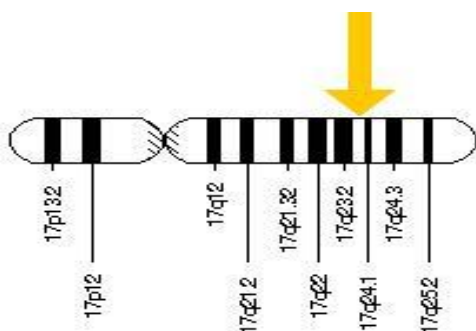


Figure 2: Voltage-gated sodium channel found at the neuromuscular junction Locus: 17q23.1-q25.3.

- These mutations are loss-of-function, such that the channels cannot open normally.
- In patients with mutations in *SCN4A* or *CACNA1S*, therefore, the channel has a reduced excitability and signals from the central nervous system are unable to depolarise the muscle. As a result, the muscle cannot contract efficiently (paralysis).
- The condition is hypokalemic because a low extracellular potassium ion concentration will cause the muscle to repolarise to the resting potential more quickly, so even if calcium conductance does occur it cannot be sustained.
- It becomes more difficult to reach the calcium threshold at which the muscle can contract, and even if this is reached then the muscle is more likely to relax.
- Because of this, the severity would be reduced if potassium ion concentrations are kept high.<sup>[24-26]</sup>

This condition is inherited in an autosomal dominant pattern (but with a high proportion of sporadic cases), which means one copy of the altered gene in each cell is sufficient to cause the disorder.

**Diagnosis:** The health care provider may suspect HypokalemicPP based on a family history of the disorder. Other clues to the disorder are muscle weakness symptoms that come and go with normal or low results of a potassium test.<sup>[27]</sup>

Between attacks, a physical examination shows nothing abnormal. Before an attack, there may be leg stiffness or heaviness in the legs.

During an attack of muscle weakness, blood potassium level is low. This confirms the diagnosis. There is no decrease in total body potassium. Blood potassium level is normal between attacks.

During an attack, muscle reflexes are decreased or absent. And muscles go limp rather than staying stiff. Muscle groups near the body, such as the shoulders and hips, are involved more often than the arms and legs.<sup>[28]</sup>

Tests that may be done include

- Electrocardiogram (ECG), which may be abnormal during attacks
- Electromyogram, which is usually normal between attacks and abnormal during attacks
- Muscle biopsy, which may show abnormalities

Other tests may be ordered to rule out other causes.

Diagnosis can be achieved through a specialized form of electromyographic (EMG) testing called the long exercise test. EMG demonstrates a reduced number of motor units and possibly myopathic abnormalities.

- This test measures the amplitude of a nerve response (called the Compound Muscle Action Potential or CMAP) for 40 to 50 minutes following a few minutes of exercise.
- An ECG or heart tracing may be abnormal during attacks.
- A muscle biopsy may show abnormalities.

- Besides the patient history or a report of serum potassium low normal or low during an attack, the long exercise test is the current standard for medical testing.
- Genetic diagnosis is often unreliable as only a few of the more common gene locations are tested, but even with more extensive testing 20–37% of people with a clinical diagnosis of hypokalemic periodic paralysis have no known mutation in the two known genes.
- The old glucose insulin challenge is dangerous and risky to the point of being life-threatening and should never be done when other options are so readily available.
- People with hypokalemic periodic paralysis are 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 distributions.
- The tendency of people with hypokalemic periodic paralysis to get paralyzed when epinephrine is released in "fight or flight" situations further adds to the temptation to misdiagnose the disorder as psychiatric.<sup>[29-32]</sup>

#### Treatment

HypoPP cannot be prevented. Because it can be inherited, genetic counseling may be advised for couples at risk of the disorder.

Treatment prevents attacks of weakness. Before an attack, there may be leg stiffness or heaviness in the legs. Doing mild exercise when these symptoms start may help prevent a full-blown attack.<sup>[33-35]</sup>

- Avoiding carbohydrate-rich meals,
- Potassium (fast & slow release)- Acute treatment – replacement of K, by drinking one of various potassium salts dissolved in water (debate exists over which, if any one in particular, is best used, but potassium chloride and bicarbonate are common).
- Carbonic anhydrase inhibitors- prevent attack recurrence or weakness and severity.
  - Acetazolamide (Diamox)
  - Dichlofenamide (Daranide)
- Aldosterone antagonists- Spironolactone (Aldactone)- to help maintain potassium levels
  - Eplerenone (Inspra)
- Potassium-sparing diuretics
  - Triamterene (Dyrenium)
  - Amiloride (Midamor)
- Potassium channel opener
  - Retigabine
- Delayed K-channel blocker
  - 3,4-diaminopyridine; 3,4-DAP

#### Prognosis

The prognosis for periodic paralysis varies, Overactivity, a diet that is not low in sodium and carbohydrates, or simply an unfortunate gene mutation can lead to a type

of chronic, low level weakness called an "abortive attack," or to permanent muscle damage.<sup>[36]</sup>

- Abortive attacks often respond to extra potassium, over carbohydrates, getting plenty of rest, increasing doses of medication and gentle daily exercise such as short walks.
- This type of damage can typically be observed via a muscle biopsy. Not even anabolic steroids can repair this type of muscular damage.
- Life span is expected to be normal, but attacks can drop potassium to levels low enough to cause life-threatening breathing problems or heart arrhythmia. Patients often report muscle pain and cognitive problems during attacks.
- Migraines occur in up to 50 % of all hypokalemic periodic paralysis patients and may include less common symptoms like phantom smells, sensitivity to light and sound or loss of words.
- Some patients will do well with extra magnesium (the body's natural ion channel blocker) or fish oil, while these same nutrients will make other patients worse. Patients and caregivers should take extreme caution with all new drugs and treatment plans.<sup>[37-40]</sup>

#### ACKNOWLEDGMENT

The authors are thankful to the management of Swami Vivekananda Institute of Pharmaceutical Sciences, Vangapally (V), Yadagirigutta (Mdl), Yadadri-Bhongir (Dt)-508286, Telangana, India, for the providing facilities.

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