

Hypokalaemic paralysis

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Summary

Hypokalaemic paralysis is a relatively uncommon but potentially life-threatening clinical syndrome. If recognised and treated appropriately, patients recover without any clinical sequelae. The syndrome of hypokalaemic paralysis represents a heterogenous group of disorders characterised clinically by hypokalaemia and acute systemic weakness. Most cases are due to familial or primary hypokalaemic periodic paralysis; sporadic cases are associated with numerous other conditions including barium poisoning, hyperthyroidism, renal disorders, certain endocrinopathies and gastrointestinal potassium losses. The age of onset, race, family history, medications, and underlying disease states can help in identifying the cause of hypokalaemic paralysis. Initial therapy of the patient with hypokalaemic paralysis includes potassium replacement and search for underlying aetiology. Further management depends on the aetiology of hypokalaemia, severity of symptoms, and duration of disease. This review presents the differential diagnosis for hypokalaemic paralysis and discusses management of the syndrome.

Keywords: hypokalaemia; periodic paralysis

Acute systemic weakness is a common complaint in the emergency department and has a wide differential diagnosis that includes neurologic, metabolic, and infectious aetiologies (box 1). Acute hypokalaemic paralysis, a clinical syndrome characterised by acute systemic weakness and low serum potassium, is a rare but treatable cause of acute weakness. Therefore, it is imperative for physicians, particularly those working in acute care settings, to be aware of this condition. Hypokalaemia is caused by a variety of disorders (box 2), while acute weakness has been reported with some but not all the causes of hypokalaemia (box 3).

The most prominent clinical features of hypokalaemia or potassium depletion are neuromuscular, although other systems, such as cardiovascular and gastrointestinal, may also be affected. Some patients complain of muscular weakness, especially of the lower extremities, while marked and generalised weakness of skeletal muscles is common with more severe potassium depletion. Very severe hypokalaemia may lead to virtually total paralysis including respiratory, bulbar and cranial musculature. Deaths from respiratory failure and arrhythmia have been reported. On physical examination, in addition to decreased motor power, the patient may demonstrate decreased or absent tendon reflexes. The sensations and level of consciousness are generally unaffected.

The cardinal laboratory manifestation is a serum potassium of less than 3.5 mmol/l during an attack, although it is usually much lower. Abnormalities in electrocardiogram (ECG) are common. The typical changes include flattening and inversion of T waves, appearance of U waves and ST segment sagging. ECG changes are, however, not well correlated with the severity of the disturbances in potassium metabolism. Symptomatology results from the increased ratio between intra- and extracellular potassium concentrations, which modifies membrane polarization and thereby alters the function of excitable tissues such as nerve and muscle. Diagnosis of hypokalaemic paralysis should be considered in any patient presenting with a sudden onset, areflexic, pure motor weakness involving one or more limbs, without alteration in the level of consciousness or sphincter function, and laboratory evidence of hypokalaemia.

Hypokalaemic paralysis results from either alteration in transcellular distribution of potassium or actual potassium depletion from renal or extrarenal losses. Most cases are due to a transcellular shift of potassium and the differential diagnosis includes familial periodic paralysis, thyrotoxic periodic paralysis, and barium poisoning.

Familial periodic paralysis (FPP)

All primary periodic paralyses have some features in common; they are all treatable and muscular weakness is reversible. Diagnosis is based upon patient history and confirmed by evaluation of serum potassium during attacks and by evaluating the response of muscle power to provocative testing with glucose, insulin, potassium, and cold.

Familial hypokalaemic periodic paralysis occurs as an autosomal dominant condition in two-thirds of cases and as sporadic cases in one-third (box 4). Symptoms begin early in life and rarely after the age of 25 years. Caucasians are the typically affected race, and males are affected more frequently. Attack frequency varies from daily to yearly and attacks last from 3-4 hours to as long as a day or more. Attacks are typically precipitated by rest or sleep and almost never occur during vigorous physical activity. Patients remain alert during the attacks.

The pathophysiology behind the paralysis is poorly understood. Muscular weakness can occur in association with hypokalaemia, normokalaemia or hyperkalaemia. It is also associated with paramyotonia congenita, myotonia congenita and generalised myotonia, ie, both hyperkalaemia and hypokalaemia can cause paralysis.

The clinical differences between hypo- and hyperkalaemic FPP are listed in box 5.¹

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Differential diagnosis of acute systemic weakness

Neurologic

- myasthenia gravis
- Lambert-Eaton syndrome
- cataplexy
- sleep paralysis associated with narcolepsy
- multiple sclerosis
- transient ischaemic attack
- hyperventilation syndrome

Metabolic/toxic

- electrolyte abnormalities
- porphyria
- medications
- botulism
- alcoholism
- opiates
- hypoglycaemic episodes
- endocrine disorders

Infectious/inflammatory

- poliomyelitis
- diphtheria
- Gullain-Barre syndrome
- polymyositis
- dermatomyositis
- acute inflammatory myopathy (viral/parasitic)

Box 1

Causes of hypokalaemia

Transcellular shift of K (no depletion)

- hypokalaemic periodic paralysis
- thyrotoxic periodic paralysis
- barium poisoning
- insulin excess
- alkalosis

Actual K depletion

Renal losses

- excessive mineralocorticoids (primary & secondary aldosteronism, licorice ingestion, glucocorticoid excess)
- renal tubular diseases (RTAs, leukaemia, Liddle's syndrome, antibiotics, carbonic anhydrase inhibitors)
- diuretics
- magnesium depletion

Extra-renal losses

- deficient dietary intake
- diarrhoea
- rectal villous adenoma
- fistulas
- ureterosigmoidostomy
- laxative abuse

Box 2

Diagnosis of familial or primary hypokalaemic periodic paralysis is established by demonstrating a low serum potassium during a paralytic attack and by excluding secondary causes of hypokalaemia. ECGs during attacks show characteristic features of hypokalaemia. Patients whose attacks are infrequent require provocative testing with glucose and insulin administration; as such tests are potentially hazardous, patients must be carefully monitored during their performance.

Although the pathogenesis of FPP remains incompletely understood, alterations in potassium regulation have been well documented. Total body potassium stores remains adequate, but serum potassium decreases due to potassium migration into muscle cells which causes the muscles to become electrically inexcitable. The exact method of potassium translocation is not known but is possibly secondary to an abnormality in muscle membrane. Recent electrophysiologic studies have suggested that the fundamental defect in hyperkalaemic periodic paralysis may involve an increase in muscle membrane sodium permeability,^{2,3} but the problem with hypokalaemic periodic paralysis is possibly a calcium channel problem. Genetic linkage data have suggested that the defect in hypokalaemic periodic paralysis may be within a dihydropteridine-binding, voltage-sensitive, skeletal muscle calcium channel.⁴

The initial treatment of a patient with hypokalaemic FPP is oral potassium supplementation (0.2–0.4 mmol/kg), repeated at 15–30-minute intervals depending on the response of the ECG, serum potassium level, and muscle strength. When patients are unable to swallow or vomiting, intravenous therapy may be necessary. The intravenous dose recommended is 20 mmol potassium chloride/100 ml normal saline hourly, while monitoring clinical status and serum potassium.⁵ Glucose in the diluent should be avoided as it can cause a further intracellular shift and reduction in serum potassium levels.⁶

Prophylaxis against recurrent periodic attacks has been successful with a wide variety of treatment modalities including 100–200 mg/day of spironolactone, and 250–750 mg/day acetazolamide.^{6,7} Acetazolamide abolishes attacks in the majority of cases. The mechanism of action of acetazolamide is not fully understood, but it may block the flux of potassium from blood into the muscle.^{6,7} The metabolic acidosis that it produces may underlie its beneficial effects. Paradoxically, acetazolamide lowers serum potassium; to achieve adequate response in some patients it may be necessary to supplement potassium and to avoid high carbohydrate meals. Chronic acetazolamide therapy may be associated with renal calculus and patients should be monitored for this complication. In some patients, attacks may not respond to acetazolamide or may even be exacerbated by it; in such patients triamterene or spironolactone may be effective.

Thyrotoxic periodic paralysis

Thyrotoxic periodic paralysis (TPP; box 6) is the most common acquired form of periodic paralysis. Orientals make up to 90% of all cases reported in the literature.^{8–10} It has also been reported in Caucasians,¹¹ native American Indians,¹² Blacks¹³ and Aborigines.¹⁴ TPP is predominantly a disease of males, the male:female ratio being 20:1.^{8,14} The usual age of onset of the disorder is similar to that of thyrotoxicosis, with the second to fourth decades being the most common.^{8,9} Rarely, there is family history of TPP.^{8,12}

Except for the findings specifically caused by the hyperthyroid state (which are frequently very subtle in patients with TPP), the clinical and biochemical features of TPP are identical to those of familial periodic paralysis. In most reports from Asian nations, it is suggested that the thyrotoxicosis is usually very obvious at the time of presentation. However, most recent reports (especially those from the US) tend to emphasize the subtlety of hyperthyroid symptoms in many patients with TPP. In a recent series reported from the Mayo Clinic, nearly half of the affected patients had only subtle signs or symptoms of hyperthyroidism, in spite of clear-cut biochemical evidence.¹⁵ Graves' disease is the most common cause of hyperthyroidism in affected patients, but any cause of thyrotoxicosis, including administration of excessive amounts of exogenous thyroid hormone, can trigger attacks of TPP in susceptible patients.

In spite of the striking clinical similarities, TPP and FPP can be differentiated on the basis of the relationship of the paralytic attacks to thyroid status. Patients with FPP have normal thyroid function, and challenge with exogenous thyroid hormone does not aggravate or worsen their symptoms. On the other hand, patients with TPP have attacks only when they are hyperthyroid. Paralytic attacks can be induced by insulin and carbohydrate administration in patients with FPP and in hyperthyroid patients with TPP, but not in patients with TPP

Differential diagnosis of hypokalaemic paralysis

Transcellular distribution of K (no depletion)

- familial periodic paralysis
- thyrotoxic periodic paralysis
- barium poisoning

Actual K depletion

Renal loss

- RTAs
- Sjögren's syndrome
- medullary sponge kidney
- chronic toluene exposure
- Fanconi's syndrome
- primary hyperaldosteronism
- others

Extra-renal loss

- celiac disease
- tropical sprue
- acute gastroenteritis
- short bowel syndrome

Box 3

Familial or primary hypokalaemic periodic paralysis

- transmitted as autosomal dominant inheritance in majority of patients
- Caucasians are the typically affected race
- symptoms begin early in life usually around puberty
- attacks are typically precipitated by rest, sleep and carbohydrate
- associated with a chromosome 1p abnormality
- diagnosis is established by demonstrating a low serum K during a paralytic attack and by excluding secondary causes of hypokalaemia
- treatment is with K supplementation
- acetazolamide is prophylactic agent of choice

Box 4

Clinical differences between hypo- and hyperkalaemic FPP

Hypokalaemic periodic paralysis

- usually comes on in puberty,
- can be precipitated or induced by carbohydrate intake
- there is no muscle stiffness
- associated with a chromosome 1p abnormality

Hyperkalaemic periodic paralysis

- usually starts in infancy
- can be precipitated or induced by fasting
- muscle can be stiff
- associated with a genetic abnormality at 17q

Box 5

who have become euthyroid.⁸ After patients with TPP have become euthyroid and symptom-free, paralytic attacks will recur if patients relapse into a thyrotoxic state.⁸

The pathogenesis of TPP is uncertain. There is evidence for a decrease in the activity of calcium pump,¹⁶ however, the exact mechanism is unknown. It appears to be different to FPP since thyroid hormone does not worsen the latter.⁹

Correction of the hyperthyroid state is the most definitive treatment for TPP. While awaiting normalisation of thyroid status following initiation of thyroid-directed therapy, avoidance of precipitating factors (extreme exertion, heavy carbohydrate intake, and alcohol ingestion) is recommended. Acute attacks may respond to potassium administration in some patients. However, recurrent attacks are not consistently prevented by prophylactic potassium administration. Since serum potassium levels are normal between paralytic attacks, the rationale for supplemental potassium on a routine basis is questionable, and the prophylactic use of potassium supplementation should be considered to be unproved. Once a hypokalaemic attack has started, however, administration of potassium is standard therapy. Treatment of underlying thyrotoxicosis abolishes attacks.^{8 9 11} Beta-adrenergic blocking agents reduce the frequency and severity of attacks while measures to control thyrotoxicosis are being instituted.^{12 17} Unlike FPP, acetazolamide is not helpful in preventing attacks and may exacerbate the attacks of paralysis in TPP.¹⁷

Barium poisoning

Barium poisoning is a rare cause of hypokalaemic paralysis (box 7). The first cases were referred to as Pa Ping disease, due to an outbreak of paralysis in the Pa Ping area of the Szechwan province of China caused by ingestion of table salt contaminated by a periodic barium salt.¹⁸ Most of the instances of acute toxicity have occurred due to ingestion of barium carbonate (rodenticide), food contaminated by barium carbonate (used in error instead of potato meal), or carelessness in handling rat poison whereby it is mixed with flour and eaten.^{19 20} Acute paralysis from inhaled barium carbonate has also been reported.²¹ A few instances of barium poisoning due to industrial accidents and suicide attempts have also occurred.^{22 23} Accidental barium poisoning cases, after ingestion of a soluble barium salt instead of insoluble barium sulphate in radiodiagnosis, has also been reported.¹⁹ The fatal dose of barium carbonate is about 0.8 g. However, barium doses as low as 0.2–0.5 mg/kg body weight, resulting from barium carbonate or chloride ingestion, have been found to produce toxicity in adults.²⁴

A shift of potassium from extracellular to intracellular fluid is the basis of acute hypokalaemia in cases of barium carbonate toxicity. The exact mechanism of hypokalaemia is not known, however, it may be due to the activation of sodium-potassium-stimulated ATPase at the cell surface causing potassium entry into the cell at the cost of extracellular fluid.²⁵ Barium is reported to block the potassium channels and thereby reduce the potassium efflux from muscles. It also competitively reduces the permeability of the cell membrane to potassium which may lead to membrane depolarization.²²

The treatment of barium-induced hypokalaemic paralysis has been intravenous potassium administration.²⁴ The potassium reverses the hypokalaemia as well as displacing barium from potassium channels, allowing it to be excreted in urine.²¹ Oral administration of sodium sulphate leads to precipitation of soluble barium carbonate as insoluble barium sulphate which is not absorbed. Intravenous sodium sulphate has been used in the management of the condition, but it may lead to renal failure due to precipitation of barium in the tubules.²⁶ Oral as well as intravenous magnesium sulphate has been used with success.^{27 28}

Renal disorders

Another major category of hypokalaemic paralysis are those conditions related to total body potassium depletion secondary to renal or extrarenal losses of potassium. The resulting hypokalaemia lowers muscle membrane resting potential and electrical excitability.² Several renal disorders have been reported to be associated with hypokalaemic paralysis, however, most cases are due to renal tubular acidosis. Hypokalaemia associated with proximal (type 2) as well as distal (type 1) renal tubular acidosis may present with paralysis. Distal renal tubular acidosis is the final common pathway for hypokalaemic paralysis in a variety of diseases including medullary sponge kidney,²⁹ Sjögren's syndrome,^{30–32} and chronic toluene exposure.^{33 34} Fanconi's syndrome associated hyperchloraemic metabolic acidosis may present as hypokalaemic paralysis.^{35 36}

Treatment of hypokalaemic paralysis associated with renal tubular acidosis requires correction of hypokalaemia. Acidosis associated with distal renal tubu-

Thyrotoxic periodic paralysis

- most common acquired cause of paralysis
- orientals are typically affected race
- predominantly disease of males
- usual age of onset second to fourth decade
- rarely, there is a family history
- findings of a hyperthyroid state are very subtle
- paralytic attacks occur only when patients are hyperthyroid
- correction of hyperthyroid state is the most definitive treatment
- acetazolamide is not helpful in preventing paralytic attacks

Box 6

Barium poisoning

- rare cause of hypokalaemic paralysis
- most of cases are due to suicidal or accidental ingestion of barium
- mechanism of hypokalaemia is transcellular shift of K
- treatment of paralysis is K replacement

Box 7

lar acidosis should be corrected.³⁷ However, in proximal renal tubular acidosis, correction of the serum bicarbonate level would only exacerbate urine potassium losses³⁸ and should therefore be avoided.

Certain other renal disorders such as water intoxication,³⁹ nephrotic syndrome,⁴⁰ diuretic phase of acute tubular necrosis,⁴¹ Barter's syndrome,⁴² treatment phase of diabetic ketoacidosis,⁴³⁻⁴⁴ chlorothiazide-associated hypokalaemia,⁴⁵ and hypokalaemia following ureterosigmoidostomy,⁴⁶⁻⁴⁷ have also been associated with paralysis.

Endocrinopathies

Primary hyperaldosteronism or Conn's syndrome presenting as hypokalaemic paralysis has also been reported.⁴⁸ It is much more commonly seen in Orientals.⁴⁹ The treatment of choice is surgical excision of the aldosterone-producing tumour.⁴⁹ Spironolactone is an alternative if surgery is not possible.⁴⁹ Pseudohyperaldosteronism induced by licorice (glycyrrhizic acid) ingestion has also been associated with hypokalaemic paralysis.⁵⁰⁻⁵¹ This effect can be seen with acute and chronic doses as small as 100–200 g of licorice per day.⁵²⁻⁵³ Carbenoxolone, a derivative of glycyrrhizic acid, has also been associated with hypokalaemic paralysis.⁵⁴⁻⁵⁵ Treatment of hypokalaemic paralysis secondary to licorice ingestion includes potassium replacement and elimination of glycyrrhizic acid from the diet.

Gastrointestinal loss

Hypokalaemic paralysis has been associated with coeliac disease,⁵⁶ tropical sprue,⁵⁷ acute gastroenteritis,⁵⁸ and malabsorption due to short bowel syndrome.⁵⁹ Any disease entity that results in renal or extrarenal potassium loss is capable of producing hypokalaemic paralysis. Clinicians should look for a secondary cause of hypokalaemia in an otherwise asymptomatic patient with an underlying disease who presents with paralysis, particularly when there are atypical metabolic features.⁴²⁻⁶⁰

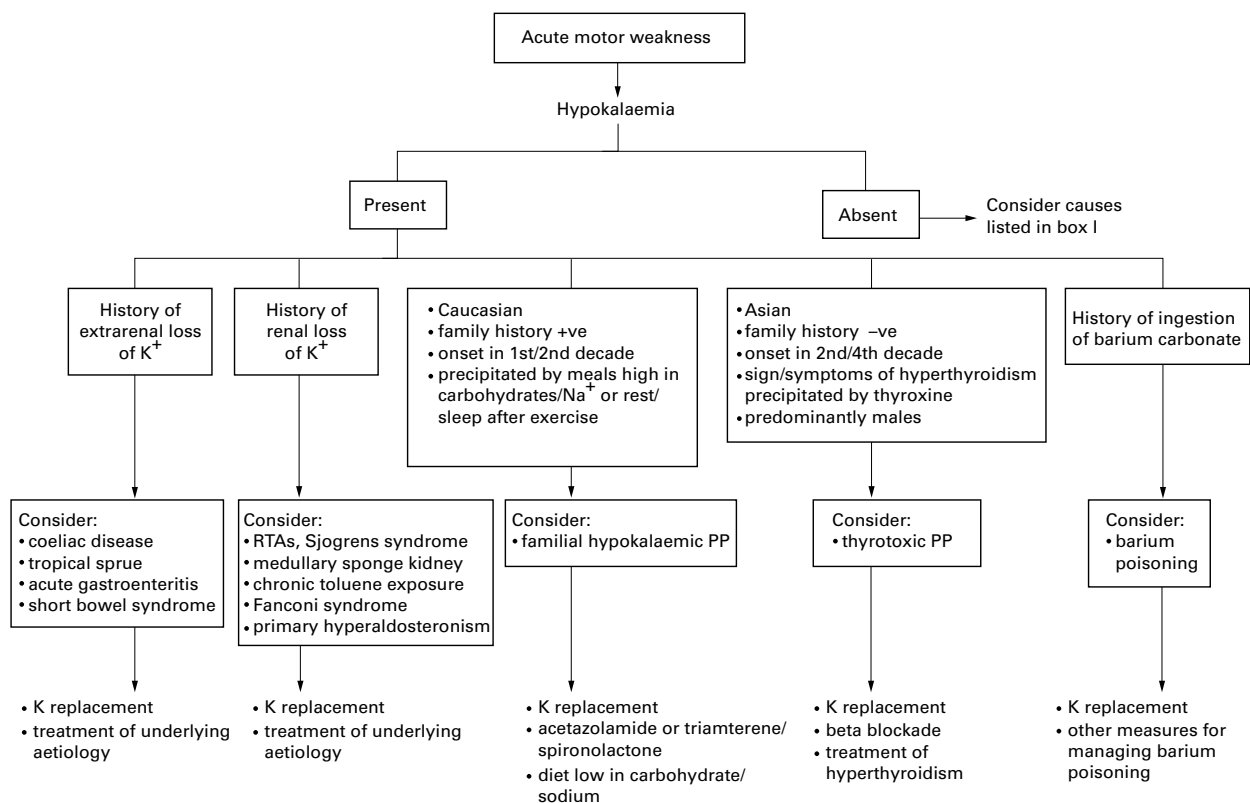


Figure 1 An approach to the patient with acute motor weakness

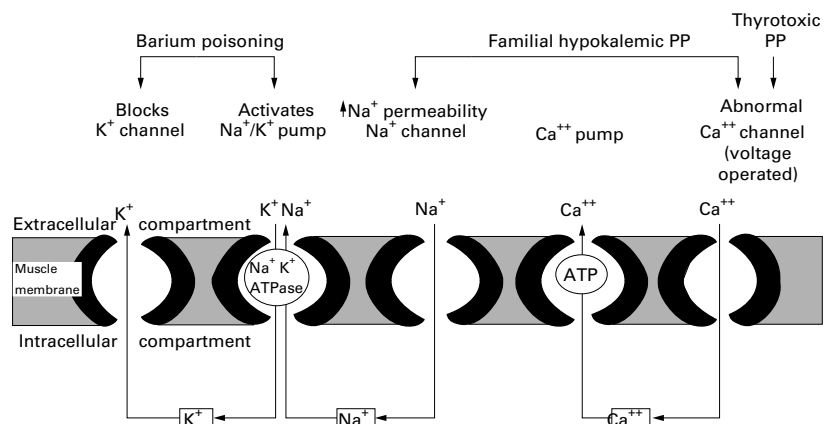


Figure 2 Pathogenesis of hypokalaemic paralysis

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