Review Article

Hypokalaemic Periodic Paralysis — A Diagnostic and Therapeutic Challenge

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Hypokalemic periodic paralysis is characterized by episodic acute onset flaccid paresis associated with hypokalemia. Classically it is a hereditary disorder with autosomal dominant inheritance causing intracellular shift of serum potassium provoked by carbohydrate or sodium load, rest after execise or certain drugs. Apart from classical hypokalaemic periodic paralysis due to inherited channelopathy, several other causes of hypokalaemia due to intracellular shift of potassium, renal or gastrointestinal loss may lead to periodic paralysis. An in-depth knowledge, thorough history and appropriate investigations are needed for underlying aetiological disorder. In this review, various aetologies, clinical features and management of hypokalemic periodic paralysis have been described with particular focus to its aetiological diagnosis.

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Key words **: Familial hypokalemic periodic paralysis, Thyrotoxic periodic paralysis, Primary hyperaldosteronism, Barter's syndrome, Gitelman's syndrome.**

Periodic paralysis (PP) is a group of rare neuromuscular disorder characterized by episodic painless acute onset flaccid muscle paresis due to muscle channelopathies. PP is classified as hypokalemic periodic paralysis (HPP) when paretic episodes are associated with low serum potassium (K^+) level. Classically HPP is a hereditary disorder with autosomal dominant inheritance pattern known as familial hypokalemic periodic paralysis (FHPP), but various other congenital and acquired causes of hypokalemia may produce similar illness manifested by episodic muscle weakness of varying frequency and intensity.

Bouts of mild to severe muscle weakness may last for hours and even days. Typically, the weakness recovers when serum K^+normalizes. Despite complete reversibility hypokalemic periodic paralysis is a medical emergency as sometimes it may cause life threatening complications like cardiac arrhythmias and respiratory muscle paralysis.Prompt and accurate etiological diagnosis is mandatory to start early interventions and to prevent the devastating outcome.FHPP is indeed the commonest etiology, but several other secondary causes of hypokalaemia should also be considered as they can also cause episodic weakness.Normal serum K^+ level in between attacks is an important feature differentiating FHPP from secondary HPP.[1]

Editor's Comment :

- Hypokalemic periodic paralysis is characterized by episodic acute onset flaccid paresis associated with hypokalemia. Classically it is a hereditary disorder with autosomal dominant inheritance causing intracellular shift of serum potassium provoked by carbohydrate or sodium load, rest after exercise or certain drugs.
- Classical hypokalaemic periodic paralysis is due to inherited channelopathy in which voltage gated calcium or sodium channels are mutated leading to intracellular shift of potassium. Apart from that, there are several other causes of hypokalaemia due to intracellular shift, renal or gastrointestinal loss of potassium.
- Thyrotoxic periodic paralysis is the second most common cause of intracellular potassium shift leading to periodic paralysis next to familial hypokalaemic periodic paralysis.
- Renal loss of potassium leading to episodic paralysis include primary hyperaldosteronism, renal tubular acidosis, Bartter's syndrome, Gitelman's syndrome, Liddle's syndrome, licorice and toluene abuse.
- Thorough history and appropriate investigations are needed for diagnosing underlying aetiological disorder. Management is based on oral potassium chloride and intravenous potassium therapy is reserved only for patients with arrythmias or respiratory muscle paralysis. Specific treatment may be required for underlying disorder.

Aetiology : Hypokalemic periodic paralysis may be classified as :

(A) Intracellular K^+shift

1. Familial hypokalemic periodic paralysis (FHPP)
2. Thyrotoxic periodic paralysis (TPP)
3. Sporadic periodic paralysis (SPP)
4. Hypothyroid periodic paralysis (HyPP)
5. Hypernatremic hypokalemic paralysis (HHP)

(B) Renal K^+ loss

1. Primary hyperaldosteroism (PH)
2. Renal tubular acidosis (RTA)
3. Barter's syndrome (BS)
4. Gitelman's syndrome (GS)
5. Liddle's syndrome (LS)

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6. Licorice ingestion
7. Toluene abuse

C. Extra-renal K^+ loss

1. Gastroenteritis
2. Zollinger Ellison syndrome
3. Fistulas

History and epidemiology :

PP was first described in 1727 by Musgrave.[2] HPP being the commonest form of PP has been described all over the world as isolated case reports as well as case series.

In a study from Taiwan by Lin et al, 97 cases with hypokalemia (serum potassium level < 3.0 meq/L) and profound muscle weaknesswere studied.[3] It was a retrospective study in Asian males over a period of 10 years. In this study, only those patients were classified as HPP who had muscle paresis due to hypokalemia as a result of intracellular shift of potassium without any acid-base disorder.Based on this criterion, seventy three out of 97 patients had HPP of which 39 had TPP, 29 had SPP, 3 had HHP and 2 had FHPP. On the other hand, 24 patients had paresis associated with hypokalemia due to kaliuresis. All of them had acid base disorder either in the form of metabolic alkalosis (PH 6, BS or GS 6, diuretic induced 3) or hyperchloremic acidosis (distal RTA 6 and toluene abuse 3).

Several case series from different parts of India were reported which implicates that HPP is not that uncommon as it is thought, rather it is under-reported. Most of the studies were done over several years. Agarwal et al described 40 cases of HPP over a period of 23 years.[4] In another series 22 cases of HPP were reported over 30 years.[5] Relatively more number of patients have been observed in a short span of 6 years in a study from south India.[6] From 1995 to 2001, 31 patients presented with HPP of which 13 had RTA, 13 had PH, 2 had TPP, 2 had sporadic HPP and 1 had GS. A study from western Odisha reported 50 cases of HPP consisting of 11 TPP, 3 hypothyroid PP, 6 SPP, 1 hypernatremic hypokalemic PP, 3 FPP, 5 distal RTA, 4 GS, 4 unidentified and 13 due to non-renal potassium loss.[7] A prospective study from North-east India reported 30 cases in 3 years.[8] A study in north-east India reported 56 patients of HPP which included 27 SPP, 5 FHPP, 4 distal RTA (d RTA),4 GS, 3 TPP, 2 HyPP.[9]

The largest study so far observed is an observational study from Midnapore, West Bengal, where among 200 cases, 56 GS, 44 d RTA 40 BS, 38 HPP, 6 TPP, 4 diuretic induced, 4 PH, 2 LS and 6 undiagnosed cases were found.[10]In this study, FHPP was associated with more frequent and recurrent episodes of periodic paralysis in comparison to HPP secondary to other causes.Recovery time was also less in FHPP compared to others.

Studies show HPP is more prevalent in summer months from April to June with dip in winter months, particularly in eastern part of India. The cause behind it is unclear. Probably, dehydration and more consumption of sweetened drink precipitates the attack.[10]

(A) HPP due to intracellular K^+ shift : HPP due to intracellular K^+ shift is typically characterized by normal acid base balance and low urinary K^+ irrespective of aetiology.

(1) Familial hypokalemic periodic paralysis (FHPP) — It is the most common HPP with a prevalence of 1 in 100,000.[11]It has autosomal dominant inheritance with incomplete penetration in females. It is 3 to 4 times more common in males than in females.FHPP is a channelopathy in which voltage-gated ion channels (typically calcium or sodium) are mutated resulting in persistent depolarization of muscle cell in presence of low potassium leading to abnormal sarcolemmal excitation and weakness. Majority of FHPP is due to mutations in either the *CACNA1S* or *SCN4A* genes, encoding the ion channels CaV1.1 (skeletal muscle L-type Ca2+ channel) and NaV1.4 (skeletal muscle voltage gated Na+ channel) respectively.[12]

Attacks typically begin in late childhood or teenage with varying frequency and duration.They may be provoked by excessive carbohydrate or sodium load in diet, rest after exercise and exposure to drugs like insulin, β2 agonists and steroids which promote shift of potassium into cells. Weakness usually involves proximal more than distal muscles and legs more than arms. Sensory, bladder and bowel involvement are usually absent. There is gross hyporeflexia or areflexia. Bulbar muscle involvement is rare.Respiratory muscles are usually spared, but rarely they may be involved to cause fatal outcome. In between attacks neurologic examination are mostly normal.

ECG findings are consistent with hypokalemia including ST segment depression, decreased amplitude of T wave and increased amplitude of U wave. Cardiac arrhythmias, such as, supraventricular tachycardia, atrial fibrillation and rarely life-threatening ventricular fibrillation may also occur due to hypokalemia.

(2) Thyrotoxic periodic paralysis (TPP) — It is a rare but well-known complication of thyrotoxicosis in Asian population including Chinese, Japanese, Vietnamese, Filipinos and Koreans. The overall incidence of TPP in Chinese and Japanese population is 1.8% and 1.9% respectively whereas its incidence is largely unknown in the West.Although thyrotoxicosis is predominantly a disease of females, TPP occurs mostly in males with a male to female ratio ranging from 17:1 to 70:1. Incidence of TPP among non-Asian hyperthyroid population, Asian hyperthyroid population and Asian hyperthyroid males are 0.1to 0.2%, 2% and 8.7 to 13% respectively.In a recent Indian study, among 244 cases of thyrotoxicosis, 15 were diagnosed as TPP. These 15 patients (14 male and 1 female) had 32 episodes of TPP. The mean age was 32± 6.2 years. Overt thyrotoxicosis was present in all cases except 1 who had subclinical hyperthyroidism.13 out of 15 patients were diagnosed as Graves' disease and the remaining 2 were subacute thyroiditis and gestational thyrotoxicosis.[13]

Unlike FHPP which occurs in younger age group (usually <20 years) and has autosomal dominant inheritance, TPP occurs at relatively later age (20-40 years) with sporadic occurrence. Pathology is not well understood but it may be due to over activation of Na^+/K^+ ATPase pump on skeletal muscle membrane due to excess thyroid hormones.Enhanced tissue responsiveness to beta

adrenergic stimulation caused by excess thyroid hormone further increases Na^+/K^+ ATPase activity.[14] In addition to enhanced adrenergic response patients having TPP have exaggerated insulin response to carbohydrate load in comparison to thyrotoxicosis patients without TPP. Insulin response sequences are present in the upstream region of Na^+/K^+ ATPase gene thus playing permissive role for intracellular K^+ shift. Often it is associated with single nucleotide polymorphism of $Ca_v1.1$ (-476A3→ G, intron 2 nt 57G→ A, intron26 nt 67A→G). Mild to moderate hypophosphatamia and mild hypomagnesaemia may accompany hypokalaemia which are due to intracellular shift of phosphate and magnesium respectively and need no separate replacement therapy. Respiratory muscles are seldom involved but total paralysis of respiratory, bulbar, and ocular muscles have been reported in a severe attack.

(3) Sporadic periodic paralysis (SPP) — It is the second common cause of HPP in Asia and has a presentation very similar to FPP but there is no family history. Few of them have same genetic mutation as FPP (*CACNA1S and SCN4A*), but most of the do not have de novo mutation. In the study from Western Odisha, out of 50 HPP patients, 6 were SPP, all of them being male. The number of SPP in this study is double the number of FPP.[7] Similarly, in the study from North East India, the number of SPP patients outnumbered FPP (SPP 27, FPP 5) out of total 56 HPP patients.[2] In Taiwan study also, out of 97 patients, 29 had SPP whereas only 2 had FPP.[3] In another Taiwan study out of 60 SPP patients, only 4 had *CACNA1S and SCN4A* mutation. SPP patients with de novo mutation usually manifest phenotype similar to FPP but with later age of onset. SPP patients without mutation also have later age of onset, but fewer attacks and lack of definite precipitating factor.[15]

(4) Hypothyroid periodic paralysis (HyPP) — It is much less common than TPP although few cases and case series have been reported. In studies from Odisha and North eastIndia, the number of HyPP are 3 and 2 respectively. In one case report, it has been postulated that hypokalemia is developed during early period of thyroxine replacement. Thyroxine in pharmacological doses can cause increased potassium excretion and water diuresis in patients with myxedema, particularly in background of malnutrition and low total potassium store in body.[16]

(5) Hypernatremichypokalemic periodic paralysis (HHP) —In Taiwan study, one unique group of patients were found, 3 out of total 97 HPP, all male, who had severe degree of hypernatremia (plasma sodium concentration 167± 5.0 mmol/L)accompanying HPP.[3] Two of them had brain tumour and one had tuberculosis with involvement of hypothalamus.Exact cause of hypokalemia in these patients are not known. Hypothalamus is an area which controls osmoregulation including thirst as well as adrenergic activity. It has been speculated that involvement of this area of brain due to some infiltrative disease or tumour impair thirst and lead to hypernatremia. It also results in hypokalemia via hyperadrenergic state which activate Na^+ K^+ ATPase activity causing transcellular shift of K+ into cell. In addition, hypernatremia has been implicated to some extent for muscle paresis.

HPP due to renal K^+ loss — HPP due to renal K+ loss is always associated with acid base disorder, either metabolic alkalosis (PH, BS, GS, LS, diuretics and licorice ingestion) or hyperchloremic metabolic acidosis (RTA, toluene abuse).

Primary hyperaldosteronism (PH) — It is also called Conn's syndrome and is characterized by overproduction of mineralocorticoid hormone aldosterone by adrenal gland.Two most common causes of Conn's syndrome is adrenal adenoma and bilateral adrenal hyperplasia followed by adrenal carcinoma and glucocorticoid remediable aldosteroism. Plasma aldosterone is not only elevated, but also non-suppresible along with suppressed plasma renin activity. Excess aldosterone causes sodium and water retention in the body and excess potassium excretion through the kidney, leading to arterial hypertension and hypokalemia.Periodic paralysis due to Conn's syndrome is relatively rare. In studies from Taiwan, north-east India,Odisha and Midnapore, the number of PH cases were 6 out of 97, 1 out of 56, 0 out of 50 and 4 out of 200 respectively showing the rarity of the entity.[3,4,8,11]

Renal tubular acidosis (RTA) — It is metabolic disorder with evidence of hypercholremic acidosis that occurs in a patient of nonazotemic renal acidification defect. Two major type of RTA are proximal RTA (pRTA) and distal RTA (dRTA). pRTA is characterized by large excretion of bicarbonate in urine that leads of hyperchloremic metabolic acidosis and alkaline urine. There is proximal absorption defect that leads aminoaciduria, phosphaturia and glycosuria. dRTA is characterized by defect of distal nephron in its ability to excrete hydrogen ion primarily due to decreased H-ATPase activity.[17] It is characterized by hypokalemia, hypercalciuria, nephrocalcinosis, and/or nephrolithiasis. Principle finding that leads to strong suspicion of RTA is metabolic acidosis, normal blood urea nitrogen level and normal GFR, alkaline or neutral urine(pH > 5.9) and inability to acidify urine below pH 5.5 after ammonium chloride load along with typical electrolyte abnormality (hyperchloraemia, hypokalaemia and hypocalcaemia) with normal anion gap. HPP is more common in patients with dRTA, mostly reported in patients with primary or secondary Sjogren's syndrome The pathophysiology of RTA in Sjogren's syndrome is debated in literature. The most common histological renal lesion is interstitial nephritis, but it is unclear whether the renal tubular defects are direct results of interstitial inflammatory process or not. The cause of renal tubular defect may be lymphocytic and plasma call infiltrate surrounding renal tubule. Hypergammaglobulinaemia may also be the cause of renal tubular dysfunction.[18] HPP due to pRTA is very rare. One case of HPP has been reported due to pRTAassociated with membranoproliferative glomerulonephritis. Till now, 16 cases of RTA with respiratory paralysis have been reported.[19]

Bartter's syndrome (BS) — It is a rare disease (1 in 1,000,000)which result from mutation affecting transport protein in the thick ascending loop of Henle (NKCC2, ROMK,C1C-KB).[20,21] It most often presents in neonatal period or early childhood with polyuria, polydipsia, salt craving and growth retardation. It is a

hereditary condition transmitted as either autosomal recessive disorder (Bartter 1 to 4) or autosomal dominant disorder (Bartter 5). Metabolic abnormalities include hypokalemia, hypochloremic metabolic alkalosis, hypercalcuria with nephrocalcinosisand mild hypomagnesemia, hyperprostaglandinaemia E and increased urinary prostaglandin excretion. Hypokalemic periodic paralysis may occur in Bartter syndrome, but it is rare. In Odisha and North east Asia series single case of BS was not found.[8,10]In Taiwan series BS and GS were mentioned in single group and there were 6 such cases.[4] BS constituted the second largest group of HPP in Midnapore study next to GS although mutation analysis was not done.[11]

Gitelman's syndrome (GS) — It is another salt-losing tubulopathy due to mutations in thiazide sensitive Na-Cl co-transporter. It is more common than Bartter's syndrome (1 in 40,000) with milder clinical course and late age of presentation. In contrast to Bartter's syndrome, Gitelman syndrome is a molecularly homogenous disorder caused by loss of function mutation in SLC12A3 gene.[22] It is distinguished from most forms of Bartter's syndrome by the presence of severe form of hypomagnesemia and hypocalciuria.[22] Hypokalaemia and metabolic alkalosis are common to both. Usual presentation of this rare syndrome is tetany or hypokalaemic periodic paralysis. In Odisha series 4 out of 50 HPP cases were GS, all of them were males. One important clue to the etiological diagnosis was definitely tetany as it was present in all 4 cases. The possible cause of tetany was metabolic alkalosis and consequent low plasma calcium in presence of hypomagnesaemia.[7] 56 among 200 cases were diagnosed as GS in Midnapore study, highest amongst all causes and distinctly larger number than any other studies.[10] But confirmation of diagnosis by mutation analysis have not been done in most of the studies.

Liddle's syndrome (LS) — It is a rare autosomaldominant form of salt-sensitive hypertensiondue to activating mutation of epithelial sodium chanel(ENaC) of distal nephron. ENaC complex is composed of 3 subunits (α, β & γ) each encoded by specific gene (*SCNN1A, SCNN1B & SCNN1G*) and consisting of 2 trasmembrane regions, 1 large extracellular domain and cytoplasmic carboxyl amino acid termini. The majority of causative mutation alter or delete a proline-rich segment (PY motif) in the carboxyl cytoplasmic tail of žorãsubunit, responsible for negative regulation of the channel resulting into its overactivation.[23] They usually present with hypertension, hypokalemia and metabolic acidosis but with low level of renin and aldosterone level. Hypokalemic periodic paralysis is rarely reported in Liddle's syndrome although myopathy is more common**.**

Licorice ingestion — Licorice induced hypokalaemia is a rare disorder first described by Revers in 1946.It is a plant product consumed as candy, French alcoholic beverages *boisson de coco***,** chewing tobacco, chewing gum,some oriental herbal preparations and some medications like *p*-aminosalisylic acid and carbonexolone sodium. The active ingradient of licorice glycyrrhizic acid causes hypokalaemia by inhibition of renal enzyme 11β hydroxysteroid dehydrogenase which is responsible for local conversion of cortisol to locally inactive cortisone.This leads to activation of renal mineralocorticoid receptors by cortisol resulting in a state of apparent mineralocorticoid excess.[24] It is a reversible condition usually recovering within days but sometimes may be sustained for several weeks according to amount consumed and individual susceptibility.Regular dailyitake of 100 mg glycyrrhizic acid produces adverse effect in susceptible individual whereas more than 400 mgper day of same causes hypokalemia with hypertension in most patients. Increased salt intake potentiate the adverse effect of glycyrrhizic acid. Critical cases with periodic paralysis, rhabdomyolysis and ventricular fibrillation leding to death have been reported.

Toluene abuse — Toluene is the most widely abused inhaled volatile drug mostly present in industrial solvent. Its deliberate inhalation due to recreational purpose known as glue sniffing is not uncommon. Chronic Toluene abuse may cause distal RTA, Fanconi's syndrome, nephrolithiasis, glomerulonephritis and Goodpasteur's syndrome. Toluene interferes with the hydrogen ion gradient in distal renal tubules either due to structural damage or inhibition of intracellular process. More precisely metabolic acidosis is caused by high rate of production of organic acids like hippuric acid and benzoic acid, the metabolites of Toluene.[25] The exact cause of hypokalemia is not known. One of the possible explanations are mineralocorticoid excess due to volume contration as a result of increased osmotic load of Hippurate and increased urine flow. Another possible mechanism iskaleuresis due to presence of poorly reabsorbed anions and low urinary chloride concentrations. Periodic paralysis may be apresentation of chrinc toluene abuse. Commonest presentation of acute toluene intoxication is also hypokalemic periodic paralysis.It is not that uncommon as it was thought previously and has high mortality rate.

HPP due to Extra-renal K^+ Loss :

This is not an uncommon entity. In western Odissa series 13 cases out of 50 were due to extra-renal K^+loss which consisted of 4diarrhoea, 5 vomiting and 4 excessive sweating.In North East India series, 2 patients had post-gastroenteritis HPP.

Approach to a Patient with HPP :

As soon as hypokalemia is detected in a patient with acute onset flaccid paresis, an attempt for etiological diagnosis is always needed by careful history and examination. The following history is helpful to diagnose the cause:

- History of similar attack before
- Family history of similar attack
- Provocating factors- heavy carbohydrate or salt load, execise followed by rest, recent stress
- History of young onset hypertension
- History of thyroid disorder
- History of recent diarrhea, vomiting, exceesive sweating
- History of offending drug- insulin, ž2 agonist, steroid, diuretics

- History of addiction or abuse- licorice, toluene
- History of nephrocalcinosis
- History of tetany

Investigations :

- Serum electrolytes- to establish hypokalemia
- ECG- to corroborate hypokalemic changes
- 24 hours urinary potassium: > 15 mmol/day is suggestive of renal loss of K^+
- Transtubular potassium gradient (TTKG): TTKG=(urine K/ plasma K) x (plasma osmolality/ urine osmolality)> 4 is suggestive of renal loss of K^+
- Arterial blood gas analysis(ABG)

- Normal acid-base balance
- HPP due to intracellular shift

Metabolic acidisis- RTA, toluene abuse

Metabolic alkalosis- PH, BS, GS, LS, diuretics, licorice

- Thyroid function test- to rule out or establish diagnosis TPP
- Plasma aldosterone/renin raio- to rule out or establish diagnosis of PH in hypertensives
- Serum calcium- hypocalcaemia in RTA, BS
- Serum magnesium- hypomagnesaemia in GS
- 24 hours urinary calcium- hypercalciuria in BS, hypocalciuria in GS
- 24 hours urinary magnesium-hypermagnesuria in GS, occasionally in BS
- Genetic tests- for FHPP, BS, GS, LS, RTA

Management :

Management consideration in hypokaaemic periodic paralysis include accurate diagnosis, proper dosage of potassium supplement in acute attacks, correct choice of diuretic for prophylaxis, maintenance therapy and identification of triggering factors. Oral potassium chloride supplementation is the preferred method of replacement. 1500 mg of potassium chloride (powder or tablet) is equivalent to 20 meq of potassium. 40-60 meq of potassium raises plasma potassium concentration by 1 to 1.5 meq/l and 135 to 160 meq of it raises the level by 2.5 to 3.5 meq/l. A suggested protocolis potassium chloride 30 meq orally every 30 minutes until serum potassium normalizes.[26]

Intravenous potassium is to be avoided whenever possible except for arrhythmias, airway compromise due to ictal dysphagia or accessory respiratory muscle paralysis. Mannitol should be used as solvent rather than dextrose or saline which are potential triggers of attacks. Caution should be taken not to use more than 10 meq at a time with a time gap of 20 to 60 minutes to avoid overshoot hyperkalaemia.[26]

Rare patients with respiratory muscle involvement need assisted ventilatory support.

For maintenance therapy, a potassium sparing diuretic is usually favoured. Commonly used aldosterone antagonists are spironolactone (100 mg daily) and eplerenone, the latter having less incidence of gynaecomastia.[26] Carbonic anhydrase inhibitor (acetazolamide 250 mg twice daily) is a suitable alternative and sometimes combination of the two is effective.[38] The patients should be counselled for avoidance of triggering factors.

Thyrotoxic periodic paralysis also requires potassium replacement, but along with that definitive therapy for thyrotoxicosis (antithyroid drugs/ radio-iodine therapy / surgery) is mandatory. Non-selective b-blocker propranolol has been reported to help in some cases.[27] Definitive therapy in Conn's syndrome is surgery for aldosterone producing adenoma and aldosterone antagonist for bilateral adrenal hyperplasia. Renal tubular acidosis is treated by potassium citrate or bicarbonate to combat hypokalaemia and metabolic acidosis at the same time. Bartter syndrome is treated with prostaglandin synthetase inhibitor indomethacin as an adjunct to potassium replacement.[28]Gitelmansyndrme primarily needs lifelong magnesium replacement and may need potassium replacement also if hypokalaemia remains uncorrected.

Limitations :

The article reviews mainly the large studies of recent past in India and other countries. The ongoing review may add some other studies in future which may contribute to better understanding and management of hypokalaemic periodic paralysis.

Conclusion

Management of HPP is really a diagnostic and therapeutic challenge. Early establishment of diagnosis and exclusion of secondary causes is important because once it is diagnosed and managed properly, it is not only fully reversible, but also helps toprevent further attack. Further long term prospective studies are needed in future to look for the efficacy of maintainance therapy.

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