Original Research Article

# Etiological spectrum of hypokalemic periodic paralysis: A prospective study at tertiary care hospital

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## Abstract

**Background:** Hypokalemic periodic paralysis (HPP) can occur due to various causes which can be either primary or secondary. Identification of these secondary causes is important so that specific therapy can be instituted and long term complications prevented. **Aim:** To analyze the common etiological factors in our setup. Identification of these factors will help us to institute a specific therapy that will prevent future complications. **Material and Methods:** A total of 32 patients admitted in the Medical and Nephrology wards with acute onset of flaccid weakness and documented serum potassium of <3.5 mEq/L during the episode were included in the study. Relevant laboratory and other investigations were done to find out the cause. **Results:** In the group with normal acid base, none of them had evidence of renal potassium loss. Those with biochemical evidence of thyrotoxicosis were diagnosed as Thyrotoxic Periodic Paralysis (TPP) and those without were diagnosed as Sporadic Periodic Paralysis (SPP). In the group with metabolic acidosis all of them had evidence of renal potassium loss. In the third group with metabolic alkalosis and renal potassium loss after carefully excluding diuretic use those with urinary chloride loss (>40 mEq/L) and hypocalciuria (<2 mg/kg) were diagnosed to have Gitelman's syndrome. In the absence of hypocalciuria Classic Bartter syndrome was diagnosed. **Conclusion:** Among the patients with Hypokalemic Periodic Paralysis two thirds of them are due to secondary causes. In our study the common causes are Idiopathic or sporadic periodic paralysis, Gitelman's / Bartter syndrome and Distal Renal Tubular Acidosis.

**Key Words:** Hypokalemic periodic paralysis, metabolic acidosis, metabolic alkalosis, Gitelman's syndrome, Classic Bartter syndrome

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## INTRODUCTION

Acute systemic weakness is a common complaint in the emergency department and has wide differential diagnosis that includes neurologic, metabolic and infectious etiologies. Acute hypokalemic periodic paralysis, is a rare but treatable cause of weakness.[1] It can be even life threatening, thus emphasizing the importance of its prompt recognition in the emergency department. Hypokalemic periodic paralysis (HPP) can occur due to various causes which can be either primary or secondary. Primary or familial HPP is associated with single gene mutations in the ion channels. Secondary HPP is associated with other demonstrable causes. Although a considerable number of cases are primary HPP, the others are due to potentially reversible causes.[2] Identification of these secondary causes is important so that specific therapy can be instituted and long term complications prevented. Contrary to common belief studies done in Indian population have shown that secondary causes are more common than primary.[2] In our study we have made an attempt to analyze the various etiological factors that appear to be common in our setup. Identification of these

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factors will help us to institute a specific therapy that will prevent future complications. We have also analyzed the metabolic profile of patients with HPP that will aid in diagnosis and treatment.

## MATERIAL AND METHODS

### Study population

All patients admitted in the Medical and Nephrology wards of a tertiary care hospital with acute onset of flaccid weakness and documented serum potassium of <3.5 mEq/L during the episode were included in the study.

A total of 32 patients were identified over a two-year study period. The data of all patients were collected and analysed prospectively.

### Clinical evaluation

A questionnaire prepared noted age, sex, ethnic origin, no. of episodes, precipitating factors, duration of illness and family history of hypokalemic periodic paralysis. History of vomiting, diahorrea, drug intake including diuretics, insulin and β2 agonists, bone pain, fractures, renal stones, dry eyes, dry mouth were also obtained specifically.

Clinical examination included a detailed neurological examination and a complete physical examination with special emphasis on blood pressure, signs of hyperthyroidism, parotid, lacrimal and thyroid enlargement.

### Laboratory investigations

The following investigations were done in all patients: Serum potassium, urea, creatinine, Blood sugar, Arterial blood gases panel comprising of pH, pO2, pCO2, sodium, potassium, bicarbonate, chloride, base excess and oxygen saturation, 24-hour urinary potassium, Thyroid function tests, Electrocardiogram and Ultrasonogram of abdomen for renal size, echoes and nephrocalcinosis. For those with metabolic alkalosis and urinary potassium loss, serum calcium, magnesium, spot urine chloride and 24-hour urine calcium were done. For those with metabolic acidosis and urinary potassium loss, early morning urine pH, X-ray KUB to rule out nephrocalcinosis, Shirmer's test, lip biopsy, SSA SSB antibody for Sjogren's syndrome, serum ceruloplasmin, urine for Bence-Jones protein and serum protein electrophoresis if indicated were done. For those with metabolic alkalosis and hypertension, plasma renin aldosterone ratio and computerized tomography of adrenals to rule out Conn's syndrome were done.

### Statistical analysis

Where possible all values were represented as mean ± SEM. One-way analysis of variance (ANOVA) was used to compare between independent variables among various groups. A p value of $< 0.05$ was considered statistically significant.

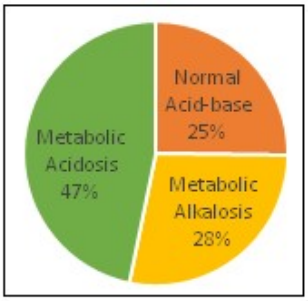
## RESULTS

There are 32 cases with the mean age of 38.44 years. Among them 18(56.25%) were males and 14(43.75%) were females. The mean age of all these patients was 38.44 (range 18-72) with 18 males and 14 females.

**Table 1:** Age distribution in groups

| Age | Normal Acid-base | | Metabolic Alkalosis | | Metabolic Acidosis | |
|---|---|---|---|---|---|---|
| | SPP | TPP | GS | BS | dRTA | Others |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| <25 years | 5 (83.33) | 0 | 0 | 0 | 1 (7.68) | 0 |
| 25-35 years | 0 | 1 (50) | 2 (28.58) | 1 (50) | 4 (30.77) | 0 |
| 35-45 years | 0 | 0 | 1 (14.28) | 1 (50) | 3 (23.07) | 0 |
| >45 years | 1 (16.67) | 1 (50) | 4 (57.14) | 0 | 5 (38.47) | 2 (100) |
| **Total** | **6 (100)** | **2 (100)** | **7 (100)** | **2 (100)** | **13 (100)** | **2 (100)** |

The mean duration of illness was 12.96 months (range 1-180). They had a mean of 2.15 episodes (range 1-10). HPP can be grouped based on acid base status in to three groups.




**Graph 1:** Major groups of HPP

In the group with normal acid base, none of them had evidence of renal potassium loss. Those with biochemical evidence of thyrotoxicosis were diagnosed as Thyrotoxic Periodic Paralysis (TPP) and those without were diagnosed as Sporadic Periodic Paralysis (SPP). In the group with metabolic acidosis all of them had evidence of renal potassium loss. In the presence of systemic acidosis, a fasting urine pH of >5.5 is taken to denote distal RTA. In the absence of systemic acidosis an ammonium chloride loading test (0.1g/kg) was done. An ultrasonogram of abdomen was done in all of these patients to rule out nephrocalcinosis and renal calculi. These patients are further worked up to rule out secondary causes of RTA. In the third group with metabolic alkalosis and renal potassium loss after carefully excluding diuretic use those with urinary chloride loss (>40 mEq/L) and hypocalciuria (<2 mg/kg) were diagnosed to haveGitelman's syndrome. Hypomagnesaemia (<1.8 mg/dl) supported the diagnosis. In the absence of hypocalciuria Classic Bartter syndrome was diagnosed.

**Table 2:** Comparison of three major groups

| Parameters | SPP (n=6) | GS (n=7) | Distal RTA (n=13) | P value | Significance |
|---|---|---|---|---|---|
| | Mean ±SD | Mean±SD | Mean±SD | | |
| Age (yrs) | 25.16±5.06 | 47±4.68 | 41.46±3.43 | 0.0116 | S |
| Age of onset (yrs) | 21.83±4.94 | 46.85±4.57 | 40.53±3.35 | 0.0030 | S |
| Duration of Illness(months) | 40.50±13.81 | 2.57±12.78 | 11.67±9.38 | 0.1764 | NS |
| Number of episodes | 2.833±0.85 | 2.28±0.78 | 2.15±0.57 | 0.2157 | NS |
| K+ (mEq/L) | 2.38±0.17 | 2.4±0.16 | 2.01±0.12 | 0.1154 | NS |
| Cl-(mEq/L) | 105.83±3.58 | 98.28±3.32 | 114.38±2.43 | 0.0024 | S |
| Urine K+ (mEq/day) | 15.26±8.50 | 71.10±7.87 | 41.50±5.77 | 0.0003 | S |

As shown above there is a statistically significant difference in the mean age, age of onset, male female ratio and urine potassium levels between the three groups. Mean age and age of onset are higher in GS group followed by dRTA group and then by SPP. Chloride levels are higher in dRTA group, normal in SPP and low normal in GS. Highest levels of renal potassium loss are seen in GS followed by dRTA whereas it is normal in SPP. Analyzing the characteristics of patients with Gitelman's syndrome, all of them had hypokalemia, metabolic alkalosis and hypocalciuria. In addition, three patients had features of tetany and four of them had hypomagnesaemia which is well known to occur in patients with Gitelman's syndrome.

**Table 3:** Characteristics of patients with Gitelman's syndrome

| Parameters | Age (yrs) | Sex | Body wt.(Kg) | Tetany | Urine Cl- | Ca2+ (mEq/L) | Mg2+ (mEq/L) | Urine Ca2+(mEq/day) |
|---|---|---|---|---|---|---|---|---|
| 1 | 50 | F | 65 | + | 72 | 5.9 | 1.27 | 116 |
| 2 | 35 | M | 60 | - | 211 | 9.4 | 2.1 | 48.3 |
| 3 | 44 | M | 70 | - | 56 | 9 | 2.2 | 120 |
| 4 | 50 | M | 71 | - | 122 | 9.4 | 0.46 | 110 |
| 5 | 33 | M | 74 | + | 103 | 7.6 | 1.1 | 128.8 |
| 6 | 66 | M | 78 | - | 86 | 8.5 | 1.4 | 112 |
| 7 | 51 | F | 59 | + | 52 | 8.8 | 1.6 | 105 |

Four of our dRTA patients had Sjogren's syndrome and their features are shown in the table 4.

**Table 4:** Analysis of Sjogren's syndrome

| Parameters | Age | Sex | Ocular and oral symptoms | Shirmer's test | SSA and SSB Ab | Lip biopsy | Renal calculi |
|---|---|---|---|---|---|---|---|
| 1 | 25 | F | + | - | + | + | + |
| 2 | 42 | F | + | - | + | + | + |
| 3 | 32 | F | + | + | + | + | + |
| 4 | 55 | F | + | + | - | + | - |

## DISCUSSION

The etiology of HPP varies in different series depending primarily on the ethnicity of population in whom it was studied. In a large retrospective study in 97 patients by Lin SH *et al*[3] from Taiwan 39 (40%) had TPP, 29 (30%) had SPP, 6 (6%) each had BS/GS and distal RTA. Overall, 66 (68%) had secondary causes of HPP. In another prospective study done in Thailand in 34 patients 15 (44%) had FPP/SPP, 11 (32%) had TPP and 8 (24%) had distal RTA.[4] Secondary causes accounted for 56% of cases. In a large retrospective series from India there were 13 patients (42%) with renal tubular acidosis, 13 with primary hyperaldosteronism (PA) (42%), 2 each with thyrotoxic periodic paralysis and sporadic periodic paralysis, and 1 with Gitelman syndrome.[5] In our study 13 (41%) had distal RTA, 7 (22%) had Gitelman's

syndrome, 6 (19%) had SPP, 2 each with TPP and Bartter syndrome, one had leptospiral ARF and one with oduvanthalai poisoning. In our series secondary causes accounted for 81% of patients.

**Table 5:** Causes of HPP in various studies

| Study | n (total) | FPP n (%) | SPP n (%) | TPP n (%) | RTA n (%) | PA n (%) | BS/GS n (%) |
|---|---|---|---|---|---|---|---|
| Lin SH *et al*[3] | 97 | 2 (2) | 29 (30) | 39 (40) | 6 (6) | 6 (6) | 6 (6) |
| Phakdeekitcharoen B *et al*[4] | 34 | 5 (15) | 10 (29) | 11 (32) | 8 (24) | 0 | 0 |
| Rao N *et al*[5] | 31 | 0 | 2 (6) | 2 (6) | 13 (42) | 13 (42) | 1 (3) |
| Our study | 32 | 0 | 6 (19) | 2 (6) | 13 (41) | 0 | 9 (28) |

Familial HPP occurs as an autosomal dominant condition in two third and sporadic in one third of patients. SPP is diagnosed in the absence of family history of periodic paralysis. In the series by Lin SH *et al* among the 97 patients 29 had SPP (23 males and 6 females) and 2 had FPP with a mean age of 26yrs.3 In another series among 34 patients 11 had SPP and 4 had FPP with the mean age of onset of 22.4yrs.[4] We also obtained the similar results in our study. All are males with mean age of 25.16 and age of onset of 21.83. Similar to Phakdeekitcharoen B *et al*[4] we also used the 24 hr urine potassium of <20 mEq/day to differentiate it from renal loss. We managed all these patients with oral potassium supplementation and acetazolamide. None of them required intravenous potassium. Two of our patients had subtle symptoms and signs of hyperthyroidism and abnormal thyroid function test. The number is similar to that reported from previous Indian study. Although TPP is reported to be common in Asian population and approximately 2% of patients with thyrotoxicosis in China and Japan are reported have TPP,[6] it is not the common cause in our study. Regional variations may play a role. In our study both the patients are males which is in agreement with other studies which says TPP affects males commonly although thyrotoxicosis is commonly seen in females. The mean age of onset is 40.50 which is higher than those with SPP. We managed both patients with oral potassium and propranolol followed by antithyroid drugs. As already pointed out by Lin SH *et al*[3] one must be careful before giving large doses of potassium supplements to these patients because they develop rebound hyperkalemia once the paralysis subsides. Distal RTA is one of major causes of HPP in our study. Although in the recent major series from India proximal RTA (32%) is more common than distal RTA (10%) in our series we found all of them to be distal RTA.5 In Lin's series3 among 97 cases studied only 6 were due to distal RTA whereas in a series from Thailand 8 among 34 patients were found to have distal RTA.4 we found that patients with distal RTA were predominantly females with mean age of 41.46 yrs. Four of our patients with distal RTA had Sjogren's syndrome. In a case series, Pun *et al* described 3 patients with Sjogren syndrome in which HPP and distal RTA preceded the diagnosis of Sjogren syndrome by 2–8 years. In this series, HPP was the presenting symptom in 3 of 26 patients with Sjogren syndrome.[7] In a western series of 16 patients with Sjogren syndrome, only 2 had RTA, but none presented with HPP. Regarding management of patients with hypokalemia and metabolic acidosis it is important point to correct hypokalemia before alkali therapy because it may aggravate the degree of hypokalemia by enhancing the movement of potassium in to cells.[3] In our series, 7 patients had features of Gitelman's syndrome and two had features of classic Bartter syndrome. Mean age in our series is 41 yrs with 6 males and three females. In Lin SH *et al*3 series there are 6 patients with Bartter/Gitelman's syndrome. Their mean age was 21 with four males and two females. There are individual case reports of Bartter syndrome presenting with hypokalemic periodic paralysis.8 Treatment of patients with Gitelman syndrome includes magnesium and potassium supplementation. Potassium-sparing diuretics and indomethacin have also been advocated.[9] It is essential to correct hypomagnesaemia simultaneously with correction hypokalemia because the hypokalemia will be resistant to correction if the underlying magnesium deficiency is not corrected. Indomethacin is the treatment of choice for patients with Bartter syndrome. Interesting fact in our study is that two patients had hypocalcaemia associated with hypomagnesaemia. We believe hypocalcaemia is probably secondary to hypomagnesaemia as highlighted in a case report.[10] One of our patients had leptospiral ARF presenting with HPP. Leptospirosis is proved by serological investigations. Renal failure recovered completely after treatment. Although it is well known that hypokalemia is frequently seen in renal involvement due to leptospirosis it is the first case presenting with quadriparesis due to hypokalemia. We had another patient who consumed oduvanthalai leaves and presented with quadriparesis and respiratory failure. He had evidence of renal potassium loss in addition to severe metabolic acidosis. This patient could not be saved even after adequate management. We had one patient with hypertension presenting with HPP. In him further investigations failed to establish the diagnosis of primary hyperaldosteronism. Although in the study by Rao N *et al* 42% of patients with HPP had primary hyperaldosteronism in our series none of them

had.[5] Three of our patients, one in the Bartter group and two in RTA group had evidence of renal dysfunction. They had normal sized kidneys with increased cortical echoes in ultasonogram. Biopsy showed features of tubulointerstitial nephritis which can occur due to chronic hypokalemia.[11] Since no other cause could be identified we believe it could be due to hypokalemic nephropathy. In rats with chronic hypokalemia, ammoniagenesis is probably stimulated because of the associated intracellular acidosis.[12] It has been suggested that a high medullary concentration of NH4+/NH3- elicits complement activation, initiating the influx of immune cells into the interstitium.[13] In a Chinese study, a case Gitelman's syndrome with renal dysfunction probably due to hypokalemic nephropathy was reported.[14] Although the long-term prognosis in preserving renal function is believed to be excellent, two patients with GS have been reported to develop end-stage renal failure requiring dialysis.[15] To prevent hypokalemia-induced nephropathy, aggressive correction of hypokalemia should be attempted.

## CONCLUSION

Among the patients with Hypokalemic Periodic Paralysis two thirds of them are due to secondary causes. In our study the common causes are Idiopathic or sporadic periodic paralysis, Gitelman's/Bartter syndrome and Distal Renal Tubular Acidosis. It is essential to correct hypokalemia before alkali therapy in patients with metabolic acidosis and to correct hypomagnesaemia along with correction of hypokalemia in patients with metabolic alkalosis.

## REFERENCES


1. The hereditary myotonias and periodic paralysis. In: Victor M, Ropper AH(eds). Adam's and Victor's principles of neurology. 7th ed. New York; McGraw Hill;2001 :1553-65.
2. Arya SN. Periodic paralysis. JIACM 2002; 3:374-82.
3. Lin SH, Lin YF, Halperin ML. Hypokalemia and paralysis. QJM 2001; 94:133-9.
4. Phakdeekitcharoen B *et al*. Hypokalemia and paralysis in the Thai population.Nephrol Dial Transplant 2004; 19:2013-18.
5. Rao N, John M, Thomas N *et al*. Aetiological, clinical and metabolic profile of hypokalemic periodic paralysis in adults. Natl Med J India 2006; 19:246-9.
6. Lin SH. Thyrotoxic periodic paralysis. Mayo Clin Proc 2005; 80:99– 105.
7. Pun KK, Wong CK, Tsui EY, Tam SC, Kung AW, Wang CC. Hypokalemic periodic paralysis due to the Sjogren syndrome in Chinese patients. Ann Intern Med 1989; 110:405–6.
8. Duman O, *et al*. Case of Bartter Syndrome Presenting With Hypokalemic Periodic Paralysis. Journal of Child Neurology 2006;21:255-6.
9. Tang NL, Hui J, To KF, Ng HK, Hjelm NM, Fok TF. Severe hypokalemic myopathy in Gitelman's syndrome. Muscle Nerve 1999;22:545-7.
10. Pantanetti P, Arnaldi G, Balercia G, Mantero F, Giacchetti G. Severe hypomagnesaemia-induced hypocalcaemia in a patient with Gitelman's syndrome. Clin Endocrinol (Oxf). 2002;56(3):413-8.
11. Schwartz WB, Relman AS. Effects of electrolyte disorders on renal Structure and function. N Engl J Med. 1967; 276:383-9.
12. Tolins JP, Hostetter MK, Hostetter TH. Hypokalemic nephropathy in the rat: role of ammonia in chronic tubular injury. J Clin Invest 1987;79:1447-58.
13. Nath KA, Hostetter MK, Hostetter TH. Increased ammoniagenesis as a determinant of progressive renal injury. Am J Kidney Dis.1991;17:654-7.
14. Lin SH, *et al*. Phenotype and Genotype Analysis in Chinese Patients with Gitelman's Syndrome. J Clin Endocrinol Metab 2005, 90:2500-7.
15. Bonfante L, Davis PA, Spinello M, Antonello A, D'Angelo A, Semplicini A, Calo L. Chronic renal failure, end-stage renal disease, and peritoneal dialysis in Gitelman's syndrome. Am J Kidney Dis 2001; 38:165-8.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