Original Article

Etiological Search and Epidemiological Profile in Patients Presenting with Hypokalemic Paresis: An Observational Study

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Abstract

Introduction: Hypokalemia is associated with increased morbidity and at times mortality. "Hypokalemic paralysis", particularly if recurrent, has often been considered synonymous with "hypokalemic periodic paralysis (HPP)"; however, diseases such as Gitelman syndrome (GS), Bartter syndrome (BS), and renal tubular acidosis (RTA) can have identical presentation. We have tried to explore the etiological spectrum along with epidemiological and certain clinical, biochemical, and electrophysiological features in patients with hypokalemic paralysis. **Materials and Methods:** In this observational study, 200 appropriate patients with hypokalemic paralysis (serum K^+ <3.5 mmol/L) were evaluated for transcellular shift, extra-renal or renal loss of K^+ as the underlying etiology of hypokalemia. We took urinary potassium >25 mmol/day as the cutoff for inappropriate renal loss of potassium in presence of hypokalemia. Serum and urinary osmolality along with arterial blood gas analysis were performed in all patients with renal loss of potassium. Serum and urinary sodium, potassium, calcium, magnesium, chloride, and creatinine were measured in normotensive patients with metabolic alkalosis. Hypertensive patients were evaluated with plasma aldosterone and renin activity. **Results:** Probable GS topped the list involving 28% individuals of the entire cohort while probable BS, distal RTA, and HPP were diagnosed in 20%, 22%, and 19% cases, respectively. Rural tribal population (61%) and age group of 30–40 years suffered the most (48%) with concentration of cases in hot and humid summer months. **Conclusions**: We suggest that patients with hypokalemic paresis should be evaluated thoroughly to unmask the underlying etiology that may have a different therapeutic and prognostic connotations and not to use the term "periodic" in cases of recurrent hypokalemic paralysis.

Keywords: Bartter syndrome, Gitelman syndrome, hypokalemic paralysis, hypokalemic periodic paralysis, Liddle syndrome, renal tubular acidosis

Introduction

Hypokalemia, conventionally defined as serum potassium ion (K^+) concentration of <3.5 mmol/L, is associated with 10-fold increase in in-hospital mortality, predominantly due to its adverse effects on the cardiovascular system. Mechanistically, hypokalemia can be caused either by redistribution of K^+ from extracellular fluid to intracellular fluid, where total body K+ remains normal or by loss of total body K^+, either renal or non-renal.[1,2]

Homeostatic mechanisms maintain the plasma potassium concentration within a narrow range (between 3.5 and 5.5 mmol/L) despite variable intake of dietary potassium. In healthy individuals, potassium excretion is mediated mainly by the kidneys (90%) and to a minor extent by the intestine and skin (10%). More than 98% of body K^+ is intracellular. Any change in total body potassium is primarily sensed by the kidneys, and they conserve potassium in hypokalemic states and excrete potassium in hyperkalemic conditions. Hence, an inappropriately high renal excretion of potassium in presence of hypokalemia suggests renal loss of potassium. In patients with hypokalemia, urine potassium excretion of more than 15 mmol/day is known to denote primary renal potassium wasting;[3] in addition, some authors have suggested urinary potassium-to-creatinine ratio of more than 13 meq/gram calculated from a twenty-four hour urinary sample as another marker of renal loss of potassium in presence of

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hypokalemia.[4] What needs to be remembered is that, these above cutoff values are valid only during hypokalemia. Oral potassium supplementation in such patients alters renal handling of potassium significantly and thus creates more confusion during etiological workup. It has recently been demonstrated that a till undiagnosed kaliuretic hormone is secreted either from the portal circulation or from the liver or gut following oral potassium intake which in turn increases renal potassium excretion even in presence of hypokalemia.[5] Hence, an inappropriately high urinary potassium excretion in hypokalemic patients having oral potassium supplementation is potentially misleading.

"Hypokalemic paralysis" seems to be considered synonymous with "hypokalemic periodic paralysis" (HPP) by majority of the primary care physicians which however is not true. HPP is undoubtedly the most common non-renal cause of hypokalemic paralysis due to redistribution of K^+ into the cells. Excess intravenous insulin therapy, long-term β2 agonists' usage in obstructive airway diseases, and thyrotoxic periodic paralysis (TPP) add to this list where hypokalemia occurs due to cellular redistribution of K^+ in individuals with normal total body K^+.[6] TPP is common in Asian population whereas HPP is common in Caucasians. Extra-renal loss of K^+ can also result in hypokalemic paralysis and example includes patients with persistent vomiting and/or diarrhea. Primary renal disorders such as Bartter syndrome (BS), Gitelman syndrome (GS), and renal tubular acidosis (RTA) are not uncommon causes of hypokalemic paralysis. Endocrinopathies such as hyperaldosteronism (both primary and secondary), Cushing syndrome, and Liddle syndrome (LS) also can have similar presentation due to renal loss of potassium. Hypertensive patients on loop or thiazide diuretics are at risk of developing hypokalemia and may at times present with paralysis. Majority of such patients (both HPP and non-HPP) usually recovers completely following appropriate treatment without any residual disability. However, if the primary pathophysiology is left unaddressed, there is a high chance of recurrence and mortality is not uncommon. For this, all patients with hypokalemic paralysis need a diligent search for possible underlying etiology and appropriate therapy to prevent further life-threatening paralytic episodes.

Majority of patients presenting with hypokalemic paralysis is stamped as HPP at the primary care level without appropriate etiological workup, which understandably is cumbersome and unfortunately a bit costly in the resource-restricted developing countries.

There is paucity of data on clinical and etiological spectrum of hypokalemic paralysis from tropical countries, and India is not an exception. A handful of studies involving relatively small number of patients have been published from India so far. We come across a large number of such patients in our institution and the average number of individuals getting hospitalized with hypokalemic paralysis per month reaches up to 50 during summer; and while handling numerous such patients in our practice, we have come across different clinical conditions presenting with hypokalemic weakness. In this cross-sectional study, we have analyzed the clinical features and possible underlying etiology of hypokalemic paralysis. People from southwestern part of West Bengal and nearby states such as Jharkhand and Odisha present to our institution. We have also tried to find out the possible precipitating factors, relations with age, ethnicity, food habits, and seasonal variations in these patients.

Materials and Methods

The study was conducted in the Department of Medicine, Midnapore Medical College and Hospital, Midnapore, West Bengal, a rural-based government hospital situated in eastern part of India. Two hundred and seventeen patients from October 2014 to September 2017 were selected for this single-center observational, cross-sectional study without any timed follow-up. Out of these patients, 14 dropped out before complete evaluation and three patients had discordant values of 24 h urinary potassium excretion in between two measurements. Data of 200 patients were finally analyzed. Patients more than 12 years of age irrespective of sex presented with acute flaccid paralysis due to hypokalemia (serum K^+ level <3.5 meq/L) and having modified Guillain–Barre disability scale of more than 2[7] were included into the study. Potassium was estimated from peripheral venous samples collected slowly with a syringe and needle (not with Vacutainer to minimize the risk of spurious hyperkalemia), avoiding fist clenching during collection, waiting at least 5 s after tourniquet release (if used) to achieve insertion of needle, and ensuring measurement of potassium within 30 min of collection. Patients with comorbid conditions such as Stage III, IV, and V chronic kidney disease (CKD) (estimated glomerular filtration rate <60 ml/min/M^2 by CKD-epidemiology collaboration formula]), chronic liver disease, chronic obstructive airway disease, congestive cardiac failure, and patients with established psychiatric and neurological diseases (Guillain–Barre syndrome, neurotoxic snake bite, myelopathy in initial shock stage) were excluded from the study. Written informed consent from each of the participants involved was obtained and approval from the Institutional Ethics Committee of Midnapore Medical College was taken.

We divided the cohort into two groups based on residence; "Rural" population referred to people living in "Panchayat" areas, and people living in municipality areas were included in the "Urban" group. We classified the food habits of the study participants according to their daily carbohydrate consumption as percentage of daily energy intake into three groups: more than 60%, 40%–60%, and <40%.

The study protocol has been summarized in Figure 1.

Serum and urine spot K+ were estimated simultaneously and a 12-lead electrocardiogram (ECG) was obtained at presentation. Patients were asked to measure 24 h urinary volume at the same time. Those having serum K^+ of <3.5 mmol/L and daily urinary

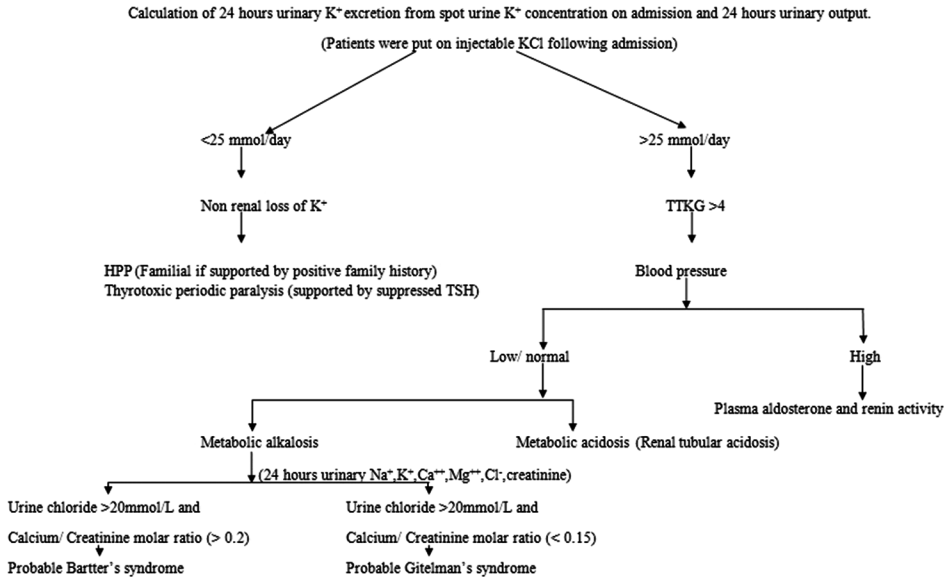

Figure 1: Summary of workup protocol

K^+ excretion of <25 mmol were further evaluated with thyroid function tests. If serum K^+ was <3.5 mmol/L and 24 h urinary K^+ was more than 25 mmol, the following investigations were performed:

1. Arterial blood gas analysis (ABG)
2. Serum potassium, sodium, calcium, albumin (for albumin-corrected calcium value), magnesium, chloride, and creatinine
3. Twenty-four hours urinary potassium, sodium, calcium, magnesium, chloride, and creatinine
4. Serum and urinary osmolality.

Transtubular potassium gradient (TTKG) was then calculated by the following equation:[3]

$$TTKG = \left(\frac{(\text{Urine } K^+ \times \text{ serum osmolality})}{(\text{Serum } K^+ \times \text{ urine osmolality})} \right)$$

If ABG denoted metabolic acidosis, simultaneous urine pH, serum and urinary anion gap, and urinary osmolal gap were measured. Oral ammonium chloride challenge test was performed in appropriate patients. We also looked for underlying collagen vascular disease (Sjogren syndrome [SS], systemic lupus erythematosus, rheumatoid arthritis) and sensorineural deafness and nephrocalcinosis/nephrolithiasis in each case of distal RTA (dRTA).

Twenty-four hours urinary samples and simultaneous serum samples for estimation of creatinine, sodium, potassium, chloride, calcium, and magnesium were sent in the normotensive metabolic alkalosis group with TTKG of more than 4. Urine creatinine levels of <1.5 g/day for men and <1 g/day for women indicate incomplete collection and the test was repeated in patients with these levels. Urinary calcium-to-creatinine molar ratio was calculated to diagnose probable BS (pBS) (ratio >0.2) and probable GS (pGS) (ratio <0.15). USG of kidneys was performed to look for any evidences of nephrocalcinosis/nephrolithiasis in cases of pBS and dRTA. We use the term pBS and pGS as we could not perform genetic studies.

In patients with metabolic alkalosis and hypertension, plasma aldosterone (PA), plasma renin activity, and direct renin concentration were measured with proper precaution. Intravenous saline loading test and adrenal imaging were performed in appropriate patients. Patients having hyperreninemic hyperaldosteronism were further evaluated with Doppler study of renal arteries. Hyporeninemic hypoaldosteronism was considered to be due to LS or Syndrome of Apparent Mineralocorticoid Excess (SAME). LS was suspected retrospectively by lack of response with spironolactone but prompt control of hypertension by amiloride, an epithelial sodium channel blockers. Unknown ingestion of liquorice was also searched for in patients with suspected SAME.

Data collected during study were entered in Microsoft Excel spreadsheet, analyzed statistically using appropriate biomedical software like SPSS for Windows 20.0 statistical package program (SPSS Inc., Chicago). As it was an observational cross-sectional study, no particular comparison was made between any groups.

Results

The demographic character of the study population is summarized in Table 1. Majority of patients was between 30 and 40 years of age, and no sex difference was observed. As far as the ethnicity and locality are concerned, rural tribal population (Listed Scheduled Tribe in Indian Constitution) constituted a large fraction of the study participants. Nearly, 88% of the study population resided in the rural area, and 61% of the entire cohort was tribal. Agricultural workers

predominated in both male and female groups and constituted 62% of the study population.

The most common preceding event of these paralytic episodes was heavy activity with profuse sweating (62% of the cohort). Interestingly, regular usual household works also precipitated hypokalemic paralysis both in females and males. However, no participant experienced the attack after prolonged rest. Carbohydrate sharing of daily energy intake of more than 60% was observed in 154 individuals (77%).

Majority of patients presented with Grade 4 paralysis on modified GBS disability scale (86%) and 39% of all patients had serum K^+ between 1.5 and 2 mmol/L at presentation [Table 2]. Interestingly GBS disability scale did not correlate with the serum potassium levels. Patients with serum potassium levels <1.5 meq/L had GBS Grade of 3 or 4 and some individuals with serum potassium >2 meq/L required assisted ventilation. Fortunately, none of the study participants died during their hospital stay. Ten patients (5%) required ventilator support and all of them recovered completely without complications or any residual disability.

The etiological spectrum of hypokalemic paralysis has been summarized in Figure 2 and Table 3. pGS topped the list (28%) followed by dRTA (22%), pBS (20%), and HPP (19%) in decreasing order of frequency. Apart from these four entities, other diseases were encountered in negligible percentages. Four of the 44 patients diagnosed with dRTA were found to have underlying SS where histology of minor salivary glands showed lymphocytic infiltration apart from objective and subjective evidences of dry eye and dry mouth. Six of these 44 individuals had history of fracture involving the lower extremities. Two middle-aged ladies with dRTA had sensorineural deafness on pure tone audiometry. The cause-specific sex ratio was not significantly different compared to the overall sex ratio in the study; however, all those patients having dRTA secondary to SS were female.

Patients of pGS and dRTA presented with much lower serum potassium values, i.e., <1.5 meq/L (20 out of 56 patients [35.7%] in pGS group, 12 out of 44 patients [27.3%] in dRTA group) whereas other diseases had comparatively higher serum potassium values at presentation [Table 4]. Serum sodium level was comparatively higher in dRTA and HPP groups than pBS and pGS groups explaining the renal salt wasting nature of the latter two entities. Both pBS and pGS had low or low normal albumin-corrected serum calcium values; however, patients with pBS had wide fluctuations in serum calcium levels (SD of 3.9). dRTA was associated with hyperchloremic normal anion gap metabolic acidosis with wide fluctuations in blood pH as well. Hypokalemia with hypertension (PH and LS) was typically associated with severe metabolic alkalosis, relatively higher serum sodium, and urinary potassium wasting. TPP and HPP were typically associated with hypokalemia only without any other biochemical alterations. Hypomagnesemia was seen among 27% and 12% of pGS and pBS cases, respectively. Mean serum magnesium was 1.1 mg/dl in the pGS group compared to 1.73 mg/dl in the pBS group [Table 5]. pGS was associated with more significant polyuria with a mean daily urinary output of 5.3 L compared to pBS (4.3 L) and dRTA (2.2 L). Serum creatine phosphokinase (CPK) was elevated in 67% of the total population with a mean CPK value of 236 ± 59.62 mg/dl among the entire cohort. It was comparatively higher in individuals with renal potassium wasting, and it did not correlate with either serum potassium levels or clinical GBS disability grading.

HPP was associated with more frequent and recurrent episodes of hypokalemic paralysis (mean number of past attack 5.36), whereas the other notable causes of hypokalemic paralysis in our study such as pGS, pBS, and dRTA had comparatively lesser number of repeated attacks with a mean number of 2.57, 3.35, and 2.68, respectively.

Table 1: Demography of the study population (*n*=200)

	Male, *n* (%)	Female, *n* (%)
Age group (years)		
12-20	14	2
20-30	18	6
30-40	58	38
40-60	32	24
>60	6	2
Total	128	72
Ethnicity		
Tribal	78 (60.9)	44 (61.1)
Nontribal	50 (39.1)	28 (38.9)
Residence		
Rural	114 (89)	62 (86.1)
Urban	14 (11)	10 (13.9)
Occupation		
Agricultural worker	98 (76.6)	26 (36.1)
Industrial worker	18 (14.1)	10 (13.9)
Self-employed	6 (4.7)	8 (11.1)
Educational worker	2 (1.5)	0
Skilled professional	0	0
Unemployed	4 (3.1)	28 (38.9)

Table 2: Serum potassium and modified Guillain-Barré syndrome disability scale at presentation

	Number of cases (*n*=200) (%)
Serum potassium value (mEq/L)	
3-3.5	4 (2)
2.5-3	26 (13)
2-2.5	54 (27)
1.5-2	78 (39)
1-1.5	30 (15)
<1	8 (4)
Modified GBS disability scale	
Grade 3	18 (9)
Grade 4	172 (86)
Grade 5	10 (5)
Grade 6	0

GBS: Guillain-Barré syndrome

The mean biochemical recovery time (restoration of normokalemia) in the study population was 4.5 ± 3.2 days following intravenous potassium supplementation. Characteristically, patients with HPP took much less time as compared to other causes for complete recovery. 19% (n = 38; pGS: 22, pBS: 12, dRTA: 4) of patients had carpopedal spasm at presentation. Bladder involvement in the form of urinary retention was an interesting finding in our study that resolved completely after restoration of normokalemia. This possibly was the result of paralysis of bladder musculature secondary to severe hypokalemia.

Table 3: Etiologies of hypokalemic paralysis of the study population (n=200)

Etiology	Total number (%)
pGS	56 (28)
dRTA	44 (22)
pBS	40 (20)
HPP	38 (19)
TPP	6 (3)
DI	4 (2)
PH	4 (2)
LS	2 (1)
U	6 (3)

pGS: probable Gitelman syndrome, dRTA: Distal renal tubular acidosis, pBS: probable Bartter, HPP: Hypokalemic periodic paralysis, TPP: Thyrotoxic periodic paralysis, DI: Diuretics induced, PH: Primary hyperaldosteronism, LS: Liddle syndrome, U: Undiagnosed/doubtful diagnosis

Discussion

Hypokalemic paralysis, first described by Musgrave in 1727,[8] is not uncommon in clinical practice. However, there is a relative paucity of data on the etiological spectrum of this

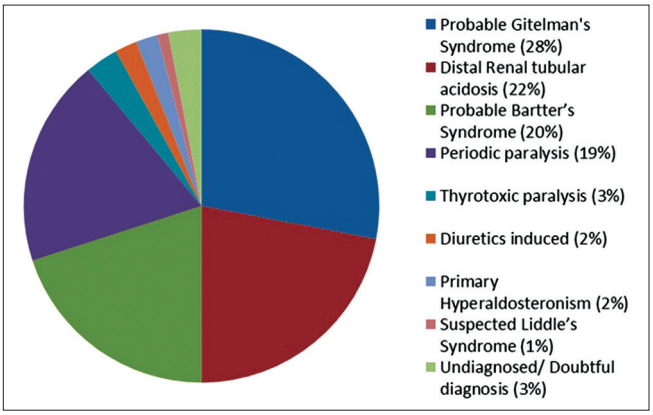

Figure 2: Etiological spectrum of hypokalemic paresis

Table 4: Disease-specific serum potassium values at presentation

Diagnosis	Serum potassium at presentation					
	3-3.5 (n=4)	2.5-3 (n=26)	2-2.5 (n=54)	1.5-2 (n=78)	1-1.5 (n=30)	<1 (n=8)
GS (n=56)	0	6	10	20	18	2
dRTA (n=44)	0	4	6	22	8	4
BS (n=40)	0	4	14	18	2	2
HPP (n=38)	0	6	14	16	2	0
TPP (n=6)	0	0	4	2	0	0
DI (n=4)	2	2	0	0	0	0
PH (n=4)	0	2	2	0	0	0
LS (n=2)	0	0	2	0	0	0
U (n=6)	2	2	2	0	0	0

GS: Gitelman syndrome, dRTA: Distal renal tubular acidosis, BS: Bartter syndrome, HPP: Hypokalemic periodic paralysis, TPP: Thyrotoxic periodic paralysis, DI: Diuretics induced, PH: Primary hyperaldosteronism, LS: Liddle syndrome, U: Undiagnosed/doubtful diagnosis

Table 5: Bio-chemical parameters at presentation in different diseases (all values are represented as mean±standard deviation)

Diagnosis	Serum Na^+ (mEq/L)	Serum K^+ (mEq/L)	Albumin corrected serum Ca^{++} (mg/dl)	Serum Cl^- (mEq/L)	Serum HCO_3 (mEq/L)	Serum pH	Urine K^+ (mEq/day)
GS (n=56)	137±2.5	1.7±0.23	8.3±0.87	97±2.67	29±4.37	7.47±0.24	45±7.6
dRTA (n=44)	143±2.67	1.56±0.46	8.7±0.43	109±6.72	15±3.76	7.26±3.56	38±6.7
BS (n=40)	136±3.36	2.04±0.62	8.1±3.9	98±5.78	28±2.89	7.51±0.34	40±8.6
HPP (n=38)	141±4.9	1.96±0.65	8.9±0.78	96±3.56	25±2.1	7.41±0.21	18±4.5
TPP (n=6)	144±1	1.75±0.25	8.8±0.33	98±1	24±1.33	7.40±0.33	14±1
DI (n=4)	123	2.9	8.5	99	27	7.42	45
PH (n=4)	143	2.5	8.9	97	38	7.52	62
LS (n=2)	145	2.2	8.8	101	27	7.45	52

GS: Gitelman syndrome, dRTA: Distal renal tubular acidosis, BS: Bartter syndrome, HPP: Hypokalemic periodic paralysis, TPP: Thyrotoxic periodic paralysis, DI: Diuretics induced, PH: Primary hyperaldosteronism, LS: Liddle syndrome

disorder. Most of the previous studies on hypokalemic paralysis had a relatively small sample size.[9-12] On the contrary, we encountered quite a large number of such patients which can be explained by the following two factors: first, the earlier studies were performed in tertiary care facilities dealing only with patients referred to them and second, people from this part of the world are either exposed to certain characteristic precipitating events or some epigenetic factors which are responsible for these hypokalemic paralysis episodes. Interestingly, earlier studies have not found an association between hypokalemic paralysis and ethnicity.[9-13] In tune with earlier evidences, we also experienced a male preponderance (64%) which can probably be explained by the fact that males generally are more exposed to physically demanding jobs outside home with more sweating particularly during the summer months and resultant loss of body potassium. We observed precipitation of paralysis following usual household works, a finding in contrast to the established literatures.[11,14]

Summer months from April to June experienced the highest concentration of paralytic episodes (79%) with significant dipping in the winter months where sweating is expectedly less compared to other seasons [Table 6]. Similar studies from the Indian subcontinent have also documented this seasonal variation, but studies from the western part of the world have not come up with similar findings. The cause of this seasonal variation is unclear; more dehydration and large consumption of sweetened drinks have been proposed to precipitate the attacks.[15] However, none of our patients had any clinical evidences of dehydration during admission. If we now look into the food habits, high carbohydrate diet was the principal feature noted in this study, and this is not unexpected as Indians are used to a carbohydrate-rich diet. Moreover, people living in this part of the country mostly consume rice at least twice a day and often thrice a day. Carbohydrate-rich diet releases more insulin from the ß-cells of the pancreas that eventually shifts potassium intracellularly, and in already potassium-depleted persons, this precipitates a paralytic attack. Contrary to the previous studies where patients aged between 20 and 30 years had suffered the most, majority of our patients were within the age group between 30 and 40 years.[9-12,16] Interestingly, individuals aged more than 60 years ($n = 8$) experienced attacks of hypokalemic paralysis also; one of them had dRTA, two had DI, and remaining five had pGS.

ECG is undoubtedly an essential tool in clinical practice, more so in critical care settings. We also looked at ECG changes in our patient population. Contrary to the classical teaching, we did not observe sequential changes of hypokalemia in ECG.

Table 6: Seasonal variation of paralytic episodes ($n = 200$)

Months	Number of cases (%)
January to March	22 (11)
April to June	158 (79)
July to September	12 (6)
October to December	8 (4)

Another interesting finding of our study was the discordance between ECG findings and the serum potassium levels. About 85% of the study participants presented with serum potassium of <2.5 meq/L but only 48% of the study population showed some kind of abnormality in their ECG. Interestingly, the prototype change of hypokalemia, i.e., appearance of "U" waves, was present only in 35% of the participants. This finding is divergent from some of the previous studies as one of them found "U" waves in every participant of hypokalemic paralysis.[13]

As far as underlying etiology of hypokalemia is concerned, pGS topped the list with 56 (28%) cases. GS had a frequency of 3.2%–13.3% of total study population in similar studies done earlier.[9-13] BS has traditionally been believed to be a disorder of childhood with growth retardations, and this entity was overlooked in the earlier studies. pBS was diagnosed in 20% of the patients in our study, and we think that an alternative diagnosis to BS was very unlikely in these patients.

The main obstacle to reach a definite diagnosis of GS and BS in our study was the lack of mutation analysis of the responsible genes. However, most of the other studies have not performed genetic study as well. We have used the term pGS and pBS because of lack of confirmatory genetic studies. Both GS and BS have almost identical biochemical abnormalities, and we used hypercalciuria (urinary calcium to creatinine molar ratio of more than 0.2 and daily urinary calcium excretion of more than 4 mg/kg/day) to differentiate pBS from pGS.[17]

GS is the result of loss-of-function mutations in the solute carrier family 12, member 3 (SLC12A3) gene which encodes the renal thiazide sensitive for sodium chloride cotransporter expressed in the apical membrane of cells in the first part of the distal convoluted tubule. BS has five subtypes, and different genes are responsible for different subtypes. Type III BS is known to occur due to mutation in the CLCNKB gene, encoding the chloride channel ClC-Kb. Interestingly in a small minority of GS patients, mutations of the same gene have been identified. It is now evident that the clinical phenotype of CLCNKB mutations can be highly variable, from an antenatal onset of BS on one end of the spectrum to a phenotype closely resembling GS at the other.[18] Hence, type III BS is an important differential diagnosis of GS, and CLCNKB gene should be screened in patients with the GS phenotype who do not have mutation in the SLC12A3 gene. Many of our patients may harbor mutation in the CLCNKB gene and may have been misclassified.

dRTA was the second most common underlying disease diagnosed in our study with a frequency of 22% ($n = 44$) which is almost double of the frequency found in earlier studies.[10,12,13] About one-fourth of these patients had nephrolithiasis and/or nephrocalcinosis. SS is a known cause of secondary dRTA, and four patients were subsequently diagnosed to have SS as per revised International Classification criteria for SS.[19] Some forms of primary dRTA are autosomal recessive and

may have hearing loss as seen in two of our patients.[20] We diagnosed 6 cases of incomplete dRTA where the patient had renal potassium wasting with normal arterial pH with the help of ammonium chloride challenge test. We did not encounter a single case of proximal RTA.

In strong contrast to earlier studies those found HPP in a substantial majority of patients, the incidence of HPP in our study was 19%.[10,12] Most of the previous studies loosely used the term "periodic" in every cases of recurrent hypokalemic paralysis; hence, comparative analysis is a bit difficult. HPP has been described as a disease of adolescents, and hypokalemic paralysis with onset after 25 years of age is said to be never due to HPP.[21] However, we came across 10 patients out of the 38 patients among HPP group who had experienced their first paralytic attack after 30 years of age, and all of them had normal thyroid functions. This particular finding we feel is unique and sparklingly contrasting to the existing literature. Positive family history (FHPP) was found only in 5.2% of the cases among HPP group; remaining cases were assumed to be sporadic in origin. TPP was diagnosed in 3% of the entire cohort, and all of them had been diagnosed with thyrotoxicosis earlier and were noncompliant with anti-thyroid drugs. They were severely thyrotoxic and experienced paralytic attack for the first time.

Six cases (3%) remained undiagnosed due to equivocal biochemical characteristics. Four of them had daily urinary potassium excretion between 15 and 25 mmol/day, and two had more than 25 mmol/day with normal arterial pH. Ammonium chloride challenge test was noncontributory in all of them. They also denied any diuretics or laxatives intake or recurrent history of vomiting or diarrhea. We suspected some remote diuretics or laxatives usage in those cases. One of the earlier studies on HPP was unable to find out the underlying cause in a large fraction of patients (38%) probably due to incomplete evaluation.[22]

We took daily urinary potassium excretion of more than 25 mmol as cutoff for renal potassium wasting. Most of the earlier studies used spot urinary potassium concentration which we feel is not appropriate while evaluating hypokalemia as there is a significant diurnal variation of renal potassium excretion. Renal potassium excretion is significantly higher in morning than in the evening. Renal wasting of potassium was confirmed in every case by repeating the test in each of the participants. We put every patient on intravenous potassium only to nullify the possible kaliuretic effect of oral potassium supplementation.[5]

There are certain limitations in our study. First of all, we did not perform genetic analysis to confirm GS and BS. Many of our patients may have been misclassified as type III BS mimics GS in every aspect. Second, diuretic screenings were not performed in the study population. It is a known fact that use of loop diuretics and thiazide diuretics closely mimics BS and GS, respectively. We focused on a thorough history and prescription screening to rule out diuretic use. We took a relatively higher cutoff for renal potassium excretion as compared to existing evidence to establish the fact that HPP is an overdiagnosed entity in patients with recurrent hypokalemic paralysis. We strongly suspect some important but yet unidentified epigenetic changes and precipitating factors in the patient population we studied. A further research looking into these issues are strongly warranted.

Conclusions

We think that HPP perhaps is the default diagnosis in patients with hypokalemic paralysis either solitary or recurrent in primary care settings across the globe and we emphasize on the fact that HPP is not synonymous with "hypokalemic paralysis." The first attack of paralysis in HPP can occur even after 25 years in certain individuals. ECG findings may not correlate with serum potassium levels, and we suggest clinicians not to rely heavily on ECG findings for diagnosis of hypokalemia; it should be used for identifying cardiac rhythm abnormalities and subsequent prognostication and as a supportive diagnostic tool in such patients. Clinical picture may not correlate with serum potassium level and treatment should be tailored taking into account serum potassium level only. Patients presenting with hypokalemia secondary to renal loss of K^+ with normal ABG analysis should be challenged with ammonium chloride to unveil underlying incomplete forms of dRTA. Last but not least, a thorough search for etiology should be undertaken in patients with hypokalemia as appropriate treatment prevents repeated attacks of potentially life-threatening dyselectrolytemia. Moreover, targeting the primary etiology prevents future complications and is cost-effective in the long run.

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Conflicts of interest

There are no conflicts of interest.

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