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Original article:

Clinical spectrum of hypokalemia associated paralysis at tertiary care center

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ABSTRACT

Introduction: Hypokalemic periodic paralysis (HPP) is relatively uncommon but potentially lethal syndrome, characterized by muscle weakness secondary to low serum potassium levels. It may be primary in origin or there may be secondary causes like thyrotoxic periodic paralysis, renal or suprarenal causes, or non-renal causes like gastroenteritis.

Aim: To study the etiology and clinical characteristics of hypokalemia associated paralysis.

Method: The study was conducted from January 2018 to June 2019. Patients fulfilling the diagnostic criteria for hypokalemic paralysis, i.e., flaccid muscle weakness involving two or more limb muscles due to serum potassium < 3.5 mmol/L and with no objective sensory signs were included in the study. Relevant investigations were done. Those with other causes of flaccid weakness or on diuretic therapy were excluded from the study.

Results: In our study, 29 patients out of a total of 50 (58%) were male, mean age of onset of HPP in maximum 64% cases were in the <35year age group, more than half had a precipitating factor. Out of 50, 35% had at least one attack before admission and most of the attacks were in the month of july (68%). In the entire sample there were 35/50 cases (70%) of secondary. Furthermore, 29/50 patients (58%) had power grade 2 or less in upper limb and 23 (46%) had power grade 2 or less in lower limb proximal muscle. The mean serum potassium during the attacks was 2.5mEq/l (range <1.4-3.9mEql/l). The 48% patients recovered within 24 hours. Only one patient died. **Conclusion:** HPP has male preponderance. Primary hypokalemic paralysis is more frequent than secondary. Renal periodic paralysis is the commonest cause of secondary periodic paralysis. HPP is an important differential in the diagnosis of acute flaccid muscle weakness. It should be promptly addressed to prevent recurrence of paralysis.

Keywords: hypokalemic periodic paralysis, low serum potassium.

Introduction

Hypokalemic periodic paralysis (HPP) is a relatively uncommon but potentially life threatening clinical syndrome. If recognized and treated appropriately, patients recover without any clinical sequelae. There are several types of Periodic Paralysis associated with metabolic and electrolyte abnormalities. The syndrome of hypokalemic paralysis represents a heterogenous group of disorders characterized clinically by hypokalemia and muscle weakness or paralysis. Hypokalemic paralysis can be primary or secondary. Hypokalemic periodic paralysis (HPP) is the most common with a prevalence of 1 in 100,000.[1]

Hypokalemic periodic paralysis (HPP), a calcium channelopathy, may be familial with autosomal dominant inheritance or sporadic.[2] Secondary causes of hypokalemic paralysis include renal causes (renal tubular acidosis, Gitelman syndrome, and primary hyperaldosteronism), endocrine causes (hyperthyroid periodic paralysis), and hypokalemia secondary to gastrointestinal losses (diarrhea).[3] Plasma potassium is normally kept at 3.5 to 5.0mEq per liter by multiple mechanisms. Hypokalemia is defined as a deficiency of potassium below 3.5mEq/L3 in the plasma and increased gastrointestinal and renal losses are the common culprits.[4] Homeostasis of this cation is tightly regulated and achieved mainly via alteration in renal excretion.[5]

The age of onset of hypokalemic periodic paralysis is mostly in the first to second decade.[6] Hypokalemic periodic paralysis is a genetic disorder caused by mutation in voltage gated calcium channel CACNA1S gene on chromosome 1q.[7] Over the past decade, mutations in genes encoding three ion channels CACN1S, SCN4, and KCNJ2 have been identified and accounted for at least 70% of cases of periodic paralysis.[7]

The clinical features of the syndrome vary somewhat depending on the underlying aetiology but the most striking feature is the sudden onset of weakness ranging in severity from mild, transient weakness to severe disability resulting in life threatening respiratory failure. HPP usually spares bulbar, ocular, and respiratory muscles. There are a multitude of factors that can trigger weakness or paralysis including acute stress, pain, anaesthesia, surgery, alcohol, strenuous exercise, heavy carbohydrate diet, or certain medications such as beta-agonists, insulin and steroids etc.[8,9] A perturbation of sodium and calcium ion channels results in low potassium levels and muscle dysfunction.[10]

As this is primarily a problem with muscle contraction rather than nerve conduction, tendon reflexes may be decreased or absent but sensation is generally intact. Although the serum potassium level is often alarmingly low, other electrolytes are usually normal. Indeed, total body potassium is actually normal with the change in the serum level reflecting a shift of potassium into cells.[11]

Although the pathogenesis of HPP remains incompletely understood, alterations in potassium regulation have been well documented. Total body potassium stores remain 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 but the problem with hypokalaemic periodic paralysis is possibly a calcium channel problem.[12] Genetic linkage data have suggested that the defect in hypokalaemic periodic paralysis may be within a dihydropteridine binding, voltage-sensitive, skeletal muscle calcium channel.[13]

Therefore, aim of this study was to evaluate cases of Hypokalemic periodic paralysis in a tertiary care center, with reference to its clinical presentations, age of incidence and prevalence, with various diagnostic and treatment modalities.

AIM

To study the etiology and clinical characteristics of hypokalemia associated paralysis.

METHODS

The prospective observational study was conducted from January 2018 to June 2019, minimum 50 patients with severe limb weakness and hypokalemia (hypokalemia associated paralysis), fulfilling the inclusion and exclusion criteria were included in the study, admitted in the department of medicine, Dayanand medical college & hospital Ludhiana. Severe limb weakness defined, as acute loss of muscle strength severe enough to prevent standing without assistance. Hypokalemia would be considered as serum potassium < 3.5 mmol/L. Diagnostic criteria for hypokalemic paralysis, i.e., flaccid muscle weakness involving two or more limb muscles due to serum potassium < 3.5 mmol/L and with no objective sensory signs. The baseline sociodemographic characteristics along with clinical presentation were documented. Relevant investigations were done. Those with other causes of flaccid weakness or on diuretic therapy were excluded from the study. The informed consent was obtained from the patients before enrolling them for clinical examination. Patients with history suggestive of diabetes mellitus, chronic kidney disease, vomiting and diarrhea, with abnormal thyroid function tests, abnormal arterial blood gas analysis, on drugs such as steroids, insulin, diuretics, salbutamol, laxatives etc. were excluded from study. A thorough clinical examination of the patient was done after taking detailed history and blood was sent for biochemical analysis such as urea, sugar, thyroid function test, and serum creatinine, serum electrolytes like sodium, potassium and magnesium. Electrocardiography was also taken simultaneously to observe changes at various levels of potassium. Finally, the different parameters like age, sex, past and family history of similar complaints, serum potassium levels and electrocardiographic changes were analysed with treatment outcomes of the patients.

RESULTS

In our study, mean age was 33.26 ±11.44 yrs with age range 15 to 60 yrs, 29 patients out of a total of 50 (29/50, i.e., 58%) were male, mean age of onset of HPP in maximum 64% cases were in the <35year age group, more than half had a precipitating factor. Most of the attacks were in between the months of July to October (68%) and maximum 36% were in August whereas there were no cases in winter season.

Table 1: SOCIO DEMOGRAPHIC PROFILE

AGE OF ONSET OF FIRST ATTACK	**NO.**	**%**
< 15	1	2
15 – 25	17	34
26 – 35	14	28
36 – 45	10	20
46 – 55	6	12
>55	2	4
SEX		
Male	29	58
Female	21	42
OCCUPATION		

Student	12	24
Labour	8	16
Housewife	15	30
Business	4	8
Employee	11	22
PRECIPITATING FACTOR		
Rest / sleep	10	20
Heavy carb. Meal	9	18
Extreme exertion	5	10
Alcohol intake	4	8
No factor	22	44
FREQUENCY OF ATTACK		
First	35	70
Second	9	18
3 or more	6	12

Table 1 shows, out of 50 patients maximum 17 (34%) were between 26-35 years of age group, 15(30%) were housewife followed by 12 (24%) students and 22% were employee in different jobs like teaching, clerical, policemen and paramedical profession. 70% had at least one attack before admission.

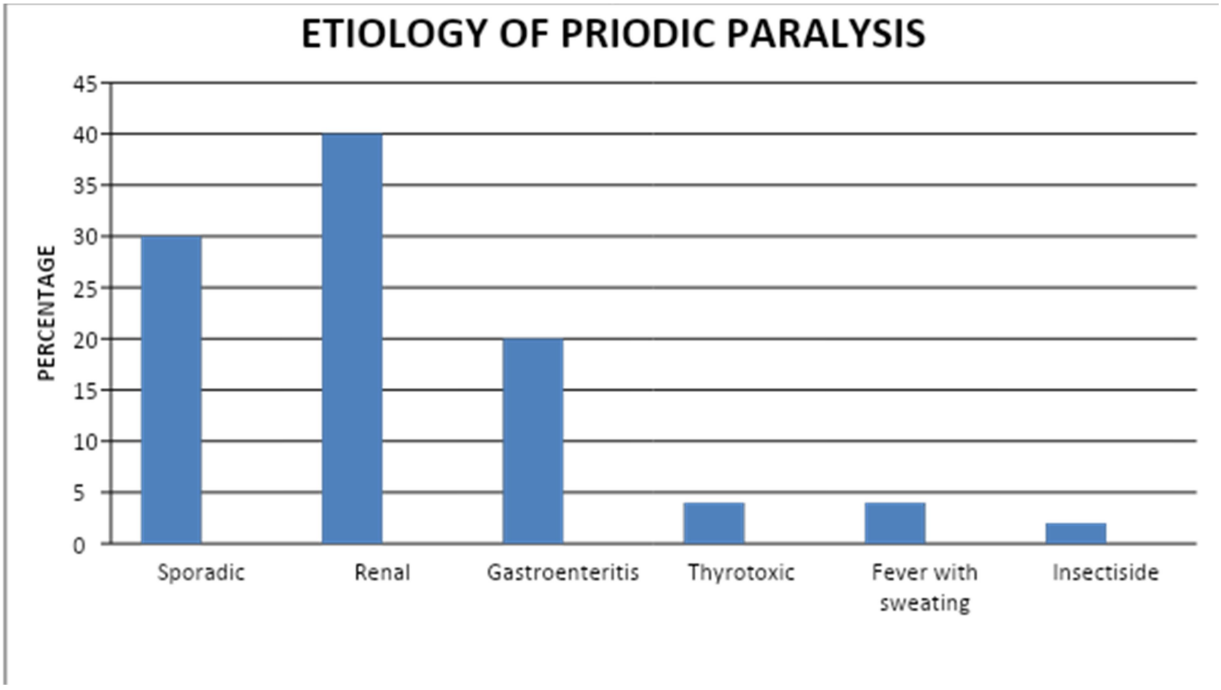
Table 2: **SIGNS AND SYMPTOMS**

GRADE OF POWER (N = 50)	**SHOULDER**	**ELBOW**	**WRIST**	**HIP**	**KNEE**	**ANKLE**
GRADE 0	8	8	8	6	8	7
GRADE 1	6	6	6	6	7	7
GRADE 2	15	13	11	11	9	7
GRADE 3	11	13	12	18	17	17
GRADE 4	10	10	13	9	9	12
GRADE 5	0	0	1	0	0	0
SINGLE BREATH COUNT		**No.**		**%**		
Not recorded		5		10		
6 – 10		2		4		
11 – 15		4		8		
16 – 20		14		28		
21 – 25		10		20		
>25		15		30		

ECG FINDINGS		
Normal sinus rhythm	28	56
U Waves	10	20
Ventricular tachycardia	2	4
AV block	2	4
Sinus tachycardia	5	10
Supraventricular bigeminy	1	2
Left ventricular hypertrophy	2	4
SERUM POTASSIUM LEVEL (mE/l)		
<1.4	4	8
1.4 – 2.5	28	56
2.6 – 3.5	16	32
>3.5	2	4

29/50 patients (58%) had power grade 2 or less in proximal muscle (shoulder) and 25 patients (50%) in distal group (wrist) in upper limb. 23 (46%) had power grade 2 or less in proximal muscle and 21 (42%) in distal muscle (foot) in lower limb. Respiratory muscle involvement was seen in five patients. Higher mental functions, cranial nerve examination and sensory examination was normal in all patients except those on ventilator support as these examinations could not be done. Single breath count was recorded in all, but 5 patients were intubated so breath count could not be recorded. The mean serum potassium of the sample during attack was 2.5mEq/l range (<1.4-3.9mEql/l). 96% patients had hypokalemia maximum 56% had 1.4 -2.5 mEq/l. At the time of admission, Two patients had >3.5 mEq/l but after repeating sample and U wave in ECG was seen, they were also found to be hypokalemic. In arterial blood gas analysis maximum 56% had metabolic acidosis while 42% were normal. 56% patients presented with hypokalemia had normal sinus rhythm.

Graph: 1



35/50 cases (70%) were of secondary hypokalemia, maximum 40% had renal cause in which 2% had proximal and 38% had distal renal tubular acidosis.

Table 3:

TIME TO RECOVERY	**No.**	**%**
<24 hrs	24	48
25 – 48 hrs	20	40
49 – 72 hrs	5	10
Expired	1	2
Length of hospital stay (LOHS)		
1 – 2 days	1	2
3 – 4 days	13	26
5 – 6 days	26	52
7 – 8 days	7	14
>8 days	3	6

The 48% patients recovered within 24 hours. Mean hospital stay was 5.7 ± 2.46 days. Only one patient died.

DISCUSSION

Weakness is a common, yet nonspecific presentation of various neurological and non-neurological conditions. While hypokalemic paralysis is an important cause of acute flaccid paralysis, various clinical differentials like acute transverse myelitis, poliomyelitis, polymyositis, porphyria, Guillain Barre syndrome should be considered. Periodic paralysis is familial or primary, but secondary causes have been seen.

A prospective observational study was conducted from january 2018 to june 2019, where 50 patients with severe limb weakness and hypokalemia, fulfilling the inclusion and exclusion criteria were included in the study, admitted in the department of medicine, Dayanand Medical College and Hospital, Ludhiana.

There are several types of period paralysis associated with metabolic and electrolyte abnormalities. Hypokalemic periodic paralysis affects approximately 1:100,000 people, with onset before 20 years of age, with the highest frequency of attacks between 15 and 35yrs of age and attack frequency decreasing thereafter.[14] In our study, mean age was 33.26 +_ 11.44 yrs with age range 15 to 60yrs, 29 patients out of a total of 50 (58%) were male. Very similarly, Rao N et al found that out of 31 patients who presented with period paralysis, 19 were men. Frequency starts diminishing by age 30 years and it rarely occurs beyond the fifth decade.[15]

Hypokalemic periodic paralysis is often precipitated by strenuous exercise or high carbohydrate meal. 18% of patients had prior history of heavy carbohydrate meal while sleep/rest was reported in 20%. Extreme exertion followed weakness in 1% of patients and alcohol consumption was noted in 8%. Other precipitants like stress, infections, lack of sleep have been reported in literature.

Most cases in our study were reported in the period from July to October (68%), with a maximum number of patients in the month of august. In the winter season, no patients were reported. El-Sonbaty MR et al reported twenty cases of hypokalemia and paralysis precipitated by hot weather.[16]

Patients experience attacks of variable severity, from mild weakness to outright paralysis, occurring at a frequency of around seven to nine episodes per month, each lasting from hours to days.[4] Our study revealed proximal muscle weakness in 58% patients with power grade 2 and distal muscle weakness was noted in 50% in the upper limb. 23 patients (46%) had power grade 2 or less in proximal muscle and 21 (42%) in distal muscles in lower limb. Sensory examination was normal in all the patients, and respiratory muscle involvement was seen in five patients. Higher mental functions and cranial nerve examination was essentially normal. There was no significant difference in grade of weakness between upper limb and lower limb as seen in other studies.[17]

Respiratory muscles were analysed by single breath count. Single breath count could not be recorded in 5 patients as they were on ventilatory support. In about 25 patients single breath count was diminished to less than 25/ min while in others it was decreased.

Common to all the periodic paralysis diseases are episodic attacks of flaccid muscle weakness, typically associated with changes in extracellular potassium during attacks(high or low), with normal potassium between attacks.[3,4] The mean serum potassium during the attacks of periodic weakness was 2.5 mEq/l and about 96% patients had documented hypokalemia. Severe hypokalemia (1.4-2.5 mEq/l) was seen in 56% cases similar to study done by Narsing R et al.[18]

Fifteen patients were diagnosed as hypokalemic periodic paralysis and classified as sporadic. Secondary hypokalemic paralysis occurred in 35 (70%) patients, with renal causes attributable in 40% of cases, sporadic in 30%, gastroenteritis in 20% cases, insecticide poisoning in 2%patients. Two patients had fever with profuse sweating leading to profound weakness. The etiology of hypokalemic paralysis is varied across different ethnicities and geographical areas.[19,20] Out of 20 patients who had renal cause, one had proximal and 19 had distal renal tubular acidosis .Ten patients had renal tubular acidosis secondary to some systemic disease. Among those with renal tubular acidosis, 4 patients were diagnosed with rheumatoid arthritis, one had underlying systemic lupus erythematosus and one patient was diagnosed as multiple myeloma. Renal tubular acidosis is a rare complication of SLE and can cause diagnostic difficulty. Renal tubular acidosis can precede or follow manifestations of SLE. Jessop et al observed impaired tubular reabsorption of phosphate and decreased urine acidification in two and seven of 12 patients with SLE respectively.[21] Our patient had a history of joint pains, swelling of small joints of hands,oral ulcers and ANA, dsDNA were positive. Patient had hypokalemia (serum potassium 1.9mEq/l), hypochloremic metabolic acidosis, urine potassium was 56mEq/l suggestive of renal potassium loss and urine pH 7.0 It is recommended to evaluate patients of hypokalemia, paralysis and distal renal tubular acidosis for any signs of autoimmune disorder. The most common identifiable autoimmune causes of RTA in adults reported are systemic lupus erythematosus, sjogren's syndrome and rheumatoid arthritis (Li SL et al, 2006)[22]

Incidence of thyrotoxic periodic paralysis is highest among asian population.Despite the higher incidence of thyrotoxic periodic paralysis in males , in our study there was one male and one female with TPP. Male preponderance of thyroid periodic paralysis is hypothesized to be due to testosterone levels in blood.[23] TPP is curable once acute thyrotoxicosis is resolved.

The important cause of hypokalemia paralysis in tropical countries is gastroenteritis .We had 10 patients with gastroenteritis(20%). Thomas SM et al .(1999) also reported 68 patients with acute quadriparesis and 70% were hypokalemic, most common cause of hypokalemia was associated with gastroenteritis (54%).[24]

LIMITATIONS OF THE STUDY

The sample size of the study was small to comment on the most frequent group as a cause of hypokalemic paralysis in our population. Transtubular potassium concentrating gradient, potassium creatinine ratio, urinary potassium, and transtubular potassium concentrating gradient during paralytic attack were not done due to the cost and non-availability of these tests at our center.

CONCLUSION

Hypokalemic paralysis should always be kept in mind when making a differential diagnosis for acute flaccid paralysis. Incidence of attack is more common in men between 25-40 years of age and 56% had potassium levels between 1.4 -2.5 mEq/l. Early diagnosis not only helps in definitive management with potassium replacement, but also prevents patient going for life threatening respiratory failure. Patients recover completely without any clinical sequellae. Further management depends on the cause, frequency of attacks, severity of symptoms and the duration of the illness.

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