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Etiological and Biochemical profile of Hypokalemic Paralysis in North-West India.

Neurology

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ABSTRACT

Hypokalemia is an important metabolic cause of acute neuromuscular weakness, which can be life threatening if not treated on time, and frequently has secondary treatable causes. Our objective was to study the etiology, clinical and biochemical features in patients of hypokalemic paralysis. 48 patients who admitted with acute flaccid paralysis with hypokalemia from September 2012 to December 2015 were included in the study and investigated thoroughly. Secondary causes were detected in 33 patients, which include renal tubular acidosis (15), thyrotoxicosis (8), diabetes mellitus (3), alcoholism and dengue fever (2 each), hypothyroidism, acute gastroenteritis, acute pyrexia (1 each). Majority (73%) patients were presented in summer season. Thus, 69% patients had secondary and potentially treatable causes which may be indicated by areflexia, higher CPK levels and if patient taking longer time to recover and precipitated by summer season and rich carbohydrate diet inherent to this part of India.

KEYWORDS:

Hypokalemia, North-West India, secondary causes.

Introduction

Hypokalemic paralysis is characterized by acute pure motor weakness of one or more limbs, without alteration in level of consciousness, and laboratory evidence of hypokalemia. It is infrequently associated with life threatening complications like respiratory paralysis and cardiac arrhythmias. Although there are large number of causes of hypokalemia in general, there are only fewer entities leading to syndrome of hypokalemic paralysis.[Ahlawat,1999] Hypokalemic periodic paralysis(HPP) is primarily a calcium or sodium channelopathy, which may be familial with autosomal dominant inheritance or sporadic. It may be due to secondary causes like thyrotoxic periodic paralysis (TPP), diarrhea, renal tubular acidosis (RTA), hyperaldosteronism and ingestion of drugs like potassium-depleting diuretics. Familial periodic paralysis (FPP) is the commonest cause in Caucasians while in Asian population TPP is the leading cause (Stedwell,1992). Thus, it is important to classify this syndrome as primary or secondary because both may be inseparable clinically but management and prognosis are different and misdiagnosis may be fatal. The varied etiologies, presentations and outcome after treatment of this syndrome are previously reported from other regions of India but not from North-West region of India, which is purpose of the present study.

Material and methods

The present study is a prospective single center study done over a period of 3 years from September 2012 to December 2015. All patients with acute flaccid weakness due to hypokalemia (serum K+ <3.5 mmol) involving one or more limbs who did not have objective sensory signs were included in the study. Patients with other causes of acute flaccid weakness on further evaluation and those on diuretic therapy were excluded.

In addition to demographic details and season of presentation, a detailed medical history including family history of similar disease was enquired and recorded. History of any precipitating event such as strenuous exercise, high carbohydrate diet was also recorded.
The examination included detailed systemic and neurologic examination including assessment of muscle tone and power using the Medical Research Council (MRC) scale, and deep tendon reflexes. Facial, bulbar and respiratory muscle weakness was also noted.

The laboratory tests, apart from complete haemogram and random blood sugar, included serum electrolytes i.e. sodium, potassium ,chloride, calcium and inorganic phosphate with renal function tests, serum creatine phosphokinase(CPK), thyroid function tests, urine pH, arterial blood gas analysis, and 12 lead electrocardiogram (ECG) in all cases. Nerve conduction studies (NCS) were performed in all cases at presentation and after recovery. In selected cases, radiography of abdomen, Glycated Hemoglobin (HbA1c), serum Immunoglobulin M antibody (IgM) and Non-structural protein-1(NS-1) detection for dengue viral infection was done.

Patients with hyperchloremic metabolic acidosis with normal anion gap, in absence of gastrointestinal loss were regarded as having RTA and classified as distal RTA if fasting urine pH <5.5 and proximal RTA if fasting urine pH >5.5. The diagnosis of distal RTA was further supported if abdominal radiography shows nephrolithiasis. (Bagga,2007) In patients with RTA, tests for antinuclear antibody (ANA), anti-dsDNA, and rheumatoid factor were carried out to find out any secondary cause.

Majority of patients were managed with oral potassium supplementation (20- 25 mEq at 6 h interval) except those having severe hypokalemia (<2.0 mM) and/or life threatening complications (respiratory, bulbar or neck flexor weakness or arrhythmias) who were treated with intravenous potassium supplementation (10 mEq /hour) and supportive care. Patients with thyrotoxicosis were additionally treated with carbimazole/methimazole and propranolol, and those with RTA were treated with oral potassium citrate. The patients with primary periodic paralysis who were having recurrent attacks were started with acetazolamide (250 mg 3 times daily), and dose was titrated as required. Patients were also advised to modify their lifestyle, especially avoidance of precipitating factors.
Data analysis was done with SPSS version 17.0. Where possible, all

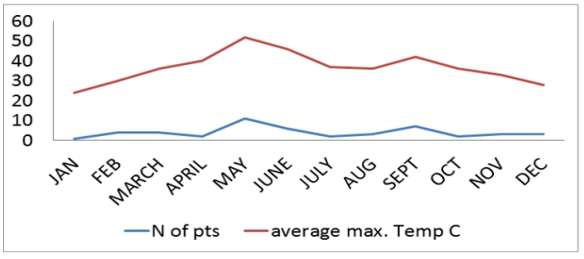
values were expressed as mean ± SD. Comparison between two groups for qualitative data was carried out by chi square and for quantitative data students T test was used. A P value < 0.05 was considered statistically significant, and a P value < 0.01 was considered statistically highly significant.

Results

48 patients with hypokalemic paralysis were included during study period of 3 years (2012-2015). Their mean age was 33.62 ± 12.84 years (range 18-85 years); male: female ratio being 2.2:1. Two patients had a family history of a similar illness.23 (47.91%) patients had a history of similar episodes in the past. Recurrent attacks were more common in the secondary group compared to primary group (33.33% vs. 54.54%) but the difference is not significant (p=0.22).

Complaints of parasthesias were reported by 2 patients and five patients had associated fever. 14 patients had myalgia, out of which 12 (85.71%) were in the secondary group, more so in RTA group. Precipitating factors included rest after exertion in 7 patients, heavy carbohydrate meal in 19, alcohol intake in 2 and gastroenteritis in 1 patient ; two patients had more than one precipitating factors. 25 (72.91%) patients presented during hot season of the year.(figure 1)

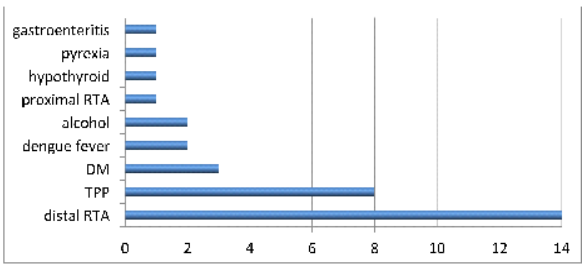
Figure 1: No. of cases /month compared to average maximum temperature



All patients reported symmetrical quadriparesis except 3 patients who had weakness limited to lower limbs. Three patients were complicated with respiratory and bulbar paralysis but none required mechanical ventilator support. Atypical presentation was identified in 12 patients in the form of neck muscles weakness (7 cases), facial weakness (2 cases) and paraparesis (3 cases). Generalized areflexia was detected in 8 patients (16.66%), hyporeflexia in 12 (25%) and 28 (58.33%) patients had normal deep tendon reflexes. Areflexia was detected only in secondary hypokalemic group which was statistically significant (p=0.04).

Hypokalemic paralysis was categorized as primary in 15 (31.25%) patients and secondary in 33 (68.75%) patients. The primary category included 2 (4.17%) cases of FPP and rest 13 (27.08%) cases were classified as sporadic periodic paralysis (SPP). The Secondary category included 15 (31.25%) cases due to RTA which further classified in distal RTA in 14 patients and proximal RTA in 1 patient. On further evaluation one patient was identified as Sjogren syndrome and one patient each had ANA positive and RA factor positive. Nephrolithiasis was present in 9 patients with distal RTA. Various other etiologies of secondary hypokalemic paralysis were identified (figure 2)

Figure 2: Etiologies of Secondary hypokalemic paralysis



The muscle weakness was more pronounced in the secondary hypokalemia group (2.55 ± 1.25) compared to the idiopathic group (2.93 ± 1.22) on MRC grade, though the difference was not significant (p=0.83).

The serum potassium concentrations were lower in patients with secondary hypokalemic paralysis (Mean ± SD 2.33± 0.62 mEq/L) as compared to primary group (Mean ± SD 2.63± 0.0.56 mEq/L) but the difference was statistically not significant (p=0.94). Conversely, the serum CPK was significantly higher in the secondary group (mean 470.27± 556.33) compared to the primary (mean 229 ± 141.35) with p value of 0.01. Electrocardiographic changes included U waves in 11 cases, ST segment sagging in 3, prolonged QTc interval in 1, and sinus tachycardia in 5 cases.

NCS showed decreased motor compound muscle action potential (CMAP) in 16 (33.33%) patients with normal sensory studies and it became normal after recovery in all patients. NCS abnormality were more pronounced in secondary hypokalemic paralysis group (10 patients) as compared to primary group (6 patients) but the difference is not significant (p=0.52).

All patients had recovery with potassium replacement therapy. The secondary group needed significantly longer time (47.85 ± 28.17 hours vs. 32.46 ±19.73 hours p= 0.02) to recover compared to the patients with primary hypokalemic paralysis. Comparison of clinical and laboratory parameters (mean ± SD) in primary and secondary hypokalemic paralysis are shown in [Table 1].

Table:1 : Comparison of various parameters of primary and secondary hypokalemic paralysis

Parametrers	Primary Hypokalemic Paralysis N=15	Secondary Hypokalemic Paralysis N=33	p Value
Age (Years)	29.27±12.42	35.60±12.72	0.057
Recurrence of Attacks	5(33.33%)	18(54.54%)	0.220
Weakness (MRC)	2.93±1.22	2.55±1.25	0.83
Absent DTR	00	08	0.04
Serum Potassium	2.63±0.56	2.33±0.62	0.94
Serum CPK Levels	229±141.35	470.27±556.332	0.01
Abnormal NCS	06	10	0.52
Time For Recovery(Hours)	32.46±19.73	47.58±30.36	0.02

Discussion

After publication of one of the largest study on HPP from Taiwan by Lin et al, 2001 in which a total of 97 cases of hypokalemic paralysis were reported over a period of 10 years, many series of HPP cases has been reported from different parts of India. This is the first series of hypokalemic paralysis from North-Western part of the India.

Male preponderance was observed in the present study, which has earlier been well documented in the Indian literature.(Rao,2006)

RTA was the leading cause of secondary hypokalemic paralysis in this study and was found in 31.25% of cases including one case of proximal RTA. In the South Indian study, RTA was the cause in 42% cases of HPP including 10 cases of proximal RTA (Rao,2006) In a study from rural northern India 69% cases had RTA as cause of hypokalemic paralysis (Kumar,2014) One of our patients had distal RTA secondary to Sjogren syndrome who, however, already had multisystem affection , hypokalemic paralysis may precede the more classic clinical findings and serves as a clinical marker for diagnosis of Sjogren syndrome.(Pous,1992)

In this study, TPP was next common cause of HPP, present in 16.67% cases. The Lin et al,2001 study had TPP in 40.2% as the etiology of hypokalemic paralysis. The earlier Indian studies has shown variable

incidence of TPP, ranging from 5.35% (Kayal,2013) to 20.6% (Garg,2013). Asian males are more often affected by this condition, with Graves' disease as most common cause. Induced Hyper adrenergic state and hyperthyroidism per se causes increased activity of Na+-K+-ATPase pump leading to hypokalemia.(Lin,2007)

Among various neurological complications hypokalemic paralysis is an important but unusual complication of dengue viral infection. In our study, 4.17% cases of hypokalemic paralysis occurred following dengue fever. Dengue fever associated hypokalemic paralysis (DHP) has been documented in up to 28% of serologically proven cases of dengue infection. (Ying,2007) Recently, a retrospective study from North India (Verma,2014) reported incidence of DHP to be 3.7%. Dengue as an etiology of hypokalemic paralysis, in Indian studies, was observed in 1.7% to 13.7% cases. (Kayal,Garg,2013) Increased plasma leakage, renal tubular impairment, stress induced hyper adrenergic and hyperinsulinemia causing redistribution of potassium into the cells and renal loss of potassium is considered to be pathophysiology of hypokalemia in dengue. (Verma,2014)

Fever per se can itself cause hypokalemic paralysis. One case in this study presented with hypokalemic paralysis occurred following acute onset high grade fever, had complete recovery after antipyretics and potassium supplementation and no other secondary cause of hypokalemia was detected. Fever induced hypokalemia may be due to low caloric intake, excessive vomiting, excessive sweating, increased adrenergic activity, secondary hyperaldosteronism due to hypovolemia leading to increased urinary and integumentary loss of potassium.(Lin,2005)

Three (6.25%) cases in this study were identified as hypokalemic paralysis secondary to uncontrolled DM. One of our patients had diabetic ketoacidosis (DKA) on presentation and rest two had severe hyperglycemia, urinary glycosuria but negative urinary ketones and all three had elevated HbA1C levels. In uncontrolled DM increased filtered glucose in renal tubules can cause osmotic diuresis leading to enhanced distal delivery of sodium and compensatory potassium secretion leading to increased renal loss of potassium.(Vishnu,2014) None of earlier studies of HPP had this causative factor and there are only rare case reports of association of hypokalemic paralysis with uncontrolled diabetes mellitus.(Amalnath,2013).

One of cases (2.08%) in this study was detected as hypokalemic paralysis secondary to hypothyroidism. The study from North-East had 3.57% cases due to hypothyroidism (Kayal,2013) This female patient had onset of illness after 35 years of age and improved with potassium and thyroid replacement and no further recurrence favored this association. Two patients (4.17%) had hypokalemic paralysis associated with alcohol intake; both were middle aged male in which no other secondary cause was identified. In the study from North East, 5.35% patients had hypokalemic paralysis after heavy alcohol intake. (Kayal,2013) Alcohol is considered as a precipitating factor for periodic paralysis and also per se can cause hypokalemia during withdrawal by increased adrenergic activity or during binge drinking by repeated vomiting and alcoholic ketoacidosis.(Ahlawat,1999)

Diarrhea is important cause of hypokalemia but hypokalemic paralysis is infrequent complication. Infectious diarrhea is attributed to be secondary cause of hypokalemic paralysis in only one (2.08%) patient in this study. Earlier Indian study had two patients (3.75%) who developed hypokalemic paralysis post gastroenteritis.(Kayal,2013) Hypokalemia due to gastrointestinal losses is usually associated with hyperchloremic non-anion gap metabolic acidosis and bicarbonate wasting and urine pH >6.
Patients with primary hypokalemic paralysis were younger than secondary group but the difference is not significant (p=0.06). This finding is similar to the study by Garg RK et al, 2013 but the difference was statistically significant in that study.

In present study common precipitating factor were high carbohydrate meal in 39.6% patients and rest after prolonged exertion in 14.5 % cases. The proportion of cases precipitated by high carbohydrate diet is quite high in present study as compared to previous studies from North-East (10.7%). (Kayal,2013) This difference can be attributed to Rajasthani meal which typically includes lots of sweets along with Baatis (Small, round breads are made of flour and deep fried) and choorma (Baatis are crushed) both served with ghee and sugar making it a high carbohydrate diet.

The muscle weakness was also more pronounced, though not significant, in the secondary group compared to the primary group (P = 0.83). However, an earlier study had also shown similar results with no significant difference. (Maurya,2010) In present study areflexia was detected in 16.66% cases and hypoactive reflexes in 25% cases. These findings are similar to the study by Garg RK et al, which showed areflexia in 17.24% and hyporeflexia in 37.93% cases. Areflexia was found only in secondary group as compared to primary group and the difference is statistically significant (p=0.04). This finding is different from previous study in which areflexia common in primary group and difference was not significant. (Garg,2013) This difference may be due to difference in population and sample size.

In our study, the serum potassium concentrations were lower, though insignificant, in patients of secondary as compared to primary hypokalemic paralysis (p = 0.94). Our finding is similar to the previous study, which also showed no significant difference in potassium values between patients of primary and secondary hypokalemic paralysis.(Lin,2001)

Atypical presentations in our study were neck muscle weakness in 14.9 % cases and 6.25% cases each had paraparesis and bilateral facial weakness. Incidence of neck weakness was reported in previous Indian studies ranging from 7.14% (Kayal,2013) Hypokalemic paraparesis was earlier reported as rare case reports but recently detected in 36 % cases in study by Mohapatra BN et al.(Mohapatra,2016) Facial paresis due to hypokalemia is very rare and previously reported in few case reports.(Sharma,2014)

In our study, Serum CPK was also significantly higher (P = 0.01) in the secondary group compared to the primary group. This finding is similar to North-East study (Kayal,2013) It is postulated that hypokalemia causes muscle ischemia, resulting in a rise in serum CPK.

NCS in hypokalemic paralysis may demonstrate decreased CMAP in midst of an attack and revert to normal after recovery.(Sharma,2014) But, this feature is reported infrequently in Indian studies. (Maurya,2010) NCS was conducted in all patients in this study and identified decreased CMAPs in 16 patients, more common in secondary group as compared to primary group but the difference is insignificant (p=0.52) and NCS became normal after recovery in all patients.

In this study, recovery with potassium replacement therapy was seen in all cases. The secondary group needed significantly longer time to recover compared to the patients with primary HPP (P = 0.02). This feature has been well documented in the literature.(Kayak,2013) This delay in recovery can be attributed to a significantly negative total body potassium balance in patients with secondary hypokalemic paralysis.

In this study 72.91% were symptomatic, without any evidence of dehydration, during the summer-autumn part of the year from the month of March to September, when the average temperature in this region ranges from 25-46°C. With the scanty and erratic rainfall and extreme summer Rajasthan witness the 'subtropical arid (dessert) climate' which is one of the factors of high prevalence of cases of hypokalemic paralysis in the summer-autumn months. These findings are consistent with earlier Indian studies, which showed high prevalence of cases of hypokalemic paralysis in the summer

season.(Kayal,2013)

There was no mortality during the entire period of this study, thereby suggesting that a timely intervention can be lifesaving in this easily treatable but potentially fatal disease.

Conclusions

In this series of hypokalemic paralysis from North-West India, 69% cases have secondary causes, reflecting higher prevalence of secondary causes and secondary cause may be indicated by Areflexia, higher CPK levels and if patient taking longer time to recover stressing need of diligent search in each such cases. This study also highlights rare presentations like facial paresis and paraparesis, along with unusual causes like uncontrolled diabetes mellitus, which has been previously reported only in isolated case reports. This study also emphasizes the value of reversible motor electrophysiological changes in this condition. Summer season and high carbohydrate diet mainly precipitate attacks reflecting need for educating the patients with Hypokalemic Paralysis to take high potassium, low carbohydrate diet especially in summer-autumn season residing or travelling to this region. Finally, we can conclude that hypokalemia is an important cause of acute flaccid paralysis, and early recognition, prompt management and lifestyle modification will give rewarding result and prevent further attacks in majority of cases.

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