A STUDY ON CLINICAL AND AETIOLOGICAL PROFILE OF HYPOKALAEMIC PARALYSIS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND

Hypokalaemic periodic paralysis is a rare disorder characterised by transient attacks of flaccid paralysis of varying intensity and frequency. Although mostly familial in aetiology, several sporadic cases with different causes have been reported. There are two groups of disorders predominantly that causes hypokalaemic paralysis. One group is due to transcellular shift of potassium and other is due to loss of potassium from body either through GI tract or through renal system.

MATERIAL AND METHODS

Here we report a study on the clinical and aetiological profile of 30 cases of hypokalaemic paralysis admitted in our institution between January 2014 to January 2016.

RESULTS

The aetiological workup of all the patients was done which revealed thyrotoxic periodic paralysis as the major cause in 12 of 30 patients. Three rare causes of hypokalaemia have been diagnosed which included Bartter's syndrome, Mixed Connective tissue disorder, Sjogren's syndrome. Vomiting and diarrhoea was seen in 12 of 30 patients.

CONCLUSION

Hypokalaemic periodic paralysis is a heterogenous group of disorder. A significant number of patients had thyroid disorders mostly in the form of thyrotoxicosis, non-renal and renal loss of potassium like diarrhoea and vomiting. Early recognition and prompt management of these conditions is essential to prevent residual deformity and further attacks in future.

KEYWORDS

Hypokalaemia, Hypokalaemic Periodic Paralysis, Thyrotoxic Periodic Paralysis (TPP), Sjogren Syndrome, Bartter's Syndrome, Mixed Connective Tissue Disorder (MCTD).

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INTRODUCTION: Hypokalaemic periodic paralysis is a rare disorder characterised by transient attacks of flaccid paralysis of varying intensity and frequency. Although mostly familial in aetiology, several sporadic cases with different causes have been reported, including some resulting from renal tubular acidosis.[1] It has been reported from different parts of the world since 1727 when the first known description of periodic paralysis was given by Musgrave.[2] There are two groups of disorders predominantly that causes hypokalaemic paralysis. One group is due to transcellular shift of potassium and other is due to loss of potassium from body either through GI tract or through renal system. In Asians, the predominant cause remains to be thyrotoxic periodic paralysis.[3]

Hypokalaemic paralysis has been underreported in neurological practice, prevalent in most parts of our country and outside. In one of the largest study on hypokalaemic flaccid paralysis from Taiwan, a total of 97 cases of hypokalaemic paralysis were reported over a period of 10 years. Here we report a clinical and aetiological workup of 30 cases of hypokalaemic paralysis admitted over a period of 2 years.

AIMS AND OBJECTIVES:

1. To study the clinical characteristics and aetiology of various cases of hypokalaemic paralysis.
2. To highlight the importance of aetiological workup and early diagnosis of hypokalaemic paralysis.

MATERIALS AND METHODS: The study was conducted over a period of 2 years between January 2014 to January 2016. 30 cases of hypokalaemic paralysis documented with decreased serum potassium and weakness were included in the study. Serum potassium of <3.5 mmol/L is taken as hypokalaemia.

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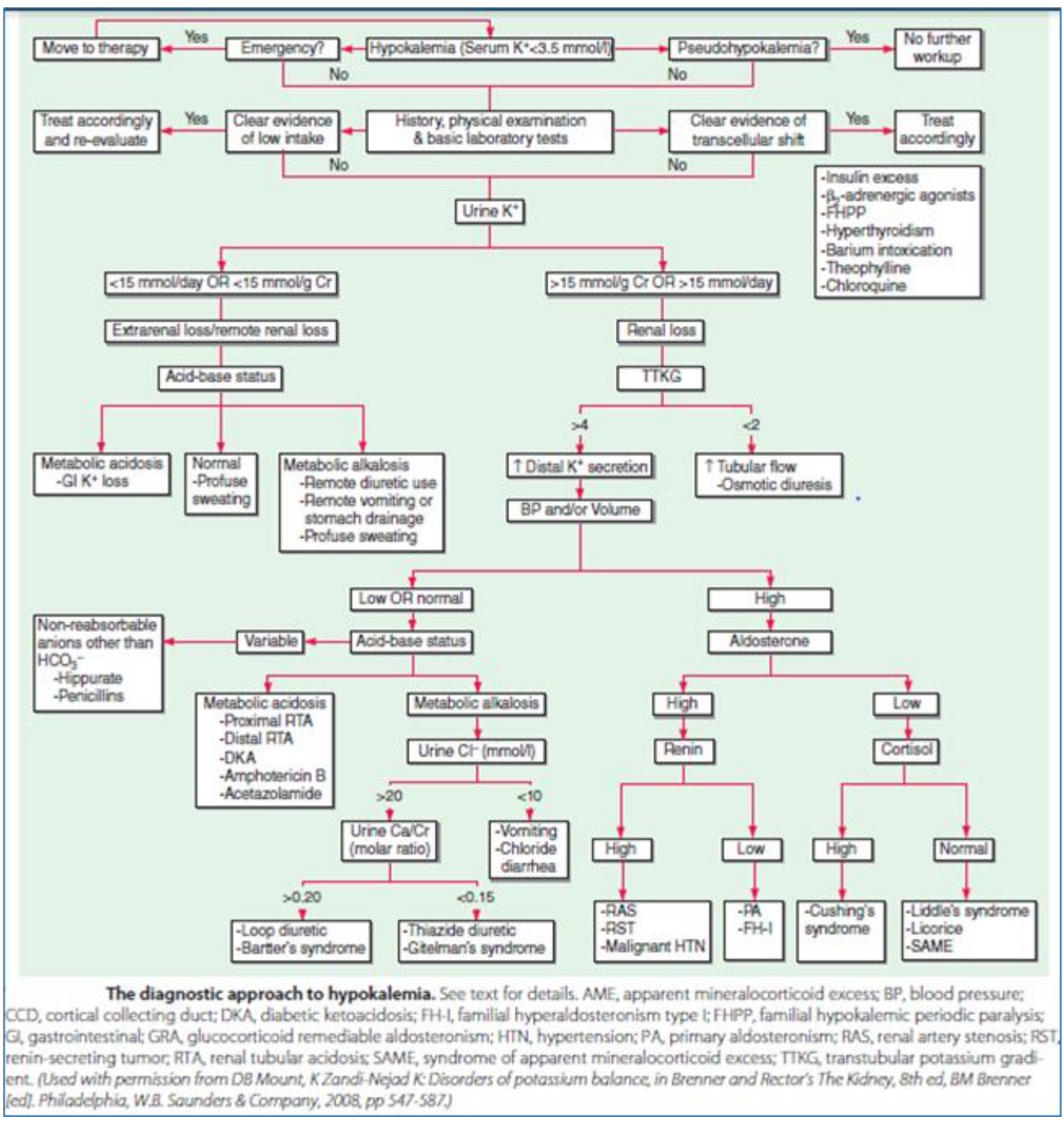
Inclusion Criteria: Patients irrespective of age and sex with documented hypokalaemia with weakness of all four limbs or both lower limbs.

Exclusion Criteria: Other etiologies of weakness like vascular (Cerebrovascular accident), demyelinating (Multiple sclerosis), polyneuropathy, myopathies, etc., are excluded from the study. All the patients were analysed with a detailed history of illness, presenting complaints, progression of illness, previous complaints & family history. Clinical evaluation was done for serum electrolytes, urine analysis for spot potassium, 24-hour potassium excretion, 24-hour urine potassium/sodium ratio, thyroid profile, Electromyography and Nerve conduction studies.

Appropriate investigations to rule out other causes have been done and necessary investigations as per the following protocol have been done in needed cases. Hypokalaemic periodic paralysis (HPP) was diagnosed if there was spot/24-hour urine potassium excretion <20 mmol/L in presence of hypokalaemia and flaccid weakness without other causes.



The diagnostic approach to hypokalemia. See text for details. AME, apparent mineralocorticoid excess; BP, blood pressure; CCD, cortical collecting duct; DKA, diabetic ketoacidosis; FH-I, familial hyperaldosteronism type I; FHPP, familial hypokalemic periodic paralysis; GI, gastrointestinal; GRA, glucocorticoid remediable aldosteronism; HTN, hypertension; PA, primary aldosteronism; RAS, renal artery stenosis; RST, renin-secreting tumor; RTA, renal tubular acidosis; SAME, syndrome of apparent mineralocorticoid excess; TTKG, transtubular potassium gradient. *(Used with permission from DB Mount, K Zandi-Nejad K: Disorders of potassium balance, in Brenner and Rector's The Kidney, 8th ed, BM Brenner (ed). Philadelphia, W.B. Saunders & Company, 2008, pp 547-587.)*

OBSERVATION AND RESULTS: Thirty cases of hypokalemic paralysis admitted in government general hospital Kurnool between January 2014 to January 2016 were studied for the clinical aspects and the etiology. The study population included age group between 19 and 60 years as minimum and maximum age with an average age of 35.3 years.

AGE DISTRIBUTION	NO. OF MALES	%	NO.OF FEMALES	%
15-20 YEARS	1	3.33	1	3.33
21-30 YEARS	4	13.33	6	20
31-40 YEARS	4	13.33	6	20
41-50 YEARS	2	6.66	2	6.66
>50 YEARS	3	10	1	3.33
TOTAL	**14(30)**		**16(30)**	

Table 1: Age and sex distribution of the study population

The patients had varied presentations with quadriplegia as the major symptomatology in 20 of 30 patients. Loss of deep tendon reflexes was seen in 20 of 30 patients and diminished DTR in 10 of 30 patients. There were no reported cases of respiratory paralysis or cranial nerve involvement.

PRESENTATION	NO. OF PATIENTS	%
QUADRIPARESIS	20(30)	66.66
PARAPARESIS	4(30)	13.3
PARAPARESIS PROGRESSING TO QUADRIPARESIS	6(30)	20
LOSS OF DEEP TENDON REFLEXES	20(30)	66.66
DIMINISHED DEEP TENDON REFLEXES	10(30)	33.33
VOMITING &/or DIARRHEA	12(30)	40
CRANIAL NERVE INVOLVEMENT	0	0
RESPIRATORY PARALYSIS	0	0

Table 2 : Clinical presentation in patients of the study group

The aetiological workup of all the patients was done which revealed thyrotoxic periodic paralysis as the major cause in 12 of 30 patients. Three rare causes of hypokalaemia has been diagnosed which included Bartter's syndrome, Mixed Connective tissue disorder, Sjogren syndrome. Vomiting and diarrhoea was seen in 12 of 30 patients.

Aetiology	No. of Patients	Age (Average)	Sex Ratio (M: F)
Thyrotoxic Periodic Paralysis	12	33.5 Y	7:5
Bartter Syndrome	1	45 Y	0:1
Mixed Connective Tissue Disorder	1	29 Y	0:1
Sjogren Syndrome	1	35 Y	0:1
Diarrhoea	5	39.4 Y	2:3
Vomiting	4	35 Y	2:2
Vomiting+ Diarrhoea	3	45 Y	2:1
Unknown	3	25.3 Y	1:2

Table 3: aetiological Profile of Patients in the Study

Sl. No	Age	Sex	Presentation	Power	Deep Tendon Reflexes	Previous Attacks	Family History	Etiology	Progression	Recovery
1	42	Male	Quadriparesis	2/5	Absent	No	No	TPP	6 Hrs.	Complete
2	39	Male	Quadriparesis	2/5	Absent	Yes	No	Diarrhoea+ Vomiting	6 Hrs.	Complete
3	40	Male	Quadriparesis	3/5	Absent	Yes	No	TPP	2 Hrs.	Incomplete
4	24	Female	Paraparesis To Quadriparesis	3/5	Absent	No	No	TPP	7 Hrs.	Complete
5	40	Female	Quadriparesis	3/5	Absent	Yes	No	Vomiting	6 Hrs.	Complete
6	42	Female	Quadriparesis	3/5	Absent	No	No	Diarrhoea	5 Hrs.	Incomplete
7	32	Female	Paraparesis To Quadriparesis	3/5	Absent	No	No	TPP	4 Hrs.	Complete
8	36	Male	Quadriparesis	3/5	Diminished	No	No	TPP	2 Hrs.	Complete
9	28	Male	Quadriparesis	3/5	Absent	No	No	TPP	2 Hrs.	Complete
10	26	Female	Quadriparesis	2/5	Diminished	No	No	Unknown	5 Hrs.	Complete

11	55	Female	Paraparesis	2/5	Absent	No	No	Diarrhoea	6 Hrs.	Complete
12	36	Male	Quadriparesis	2/5	Absent	No	No	TPP	5 Hrs.	Complete
13	24	Female	Quadriparesis	1/5	Absent	Yes	No	Diarrhoea	4 Hrs.	Complete
14	29	Female	Quadriparesis	3/5	Absent	Yes	No	Vomiting	5 Hrs.	Incomplete
15	60	Male	Parapaesis To Quadriparesis	3/5	Diminished	No	No	Diarrhoea+ Vomiting	6 Hrs.	Complete
16	24	Male	Paraparesis	3/5	Absent	No	Yes	TPP	8 Hrs.	Complete
17	32	Female	Quadriparesis	3/5	Absent	No	No	TPP	6 Hrs.	Complete
18	19	Female	Quadriparesis	3/5	Absent	No	No	TPP	7 Hrs.	Incomplete
19	29	Female	Quadriparesis	1/5	Diminished	No	No	MCTD	5 Hrs.	Incomplete
20	26	Male	Paraparesis To Quadriparesis	2/5	Diminished	No	No	Unknown	1 Hr.	Complete
21	45	Female	Quadriparesis	3/5	Diminished	No	No	Bartter's Syndrome	4 Hrs.	Complete
22	35	Female	Quadriparesis	3/5	Diminished	Yes	No	TPP	5 Hrs.	Complete
23	19	Male	Quadriparesis	3/5	Absent	No	No	Vomiting	3 Hrs.	Incomplete
24	52	Male	Paraparesis	3/5	Absent	Yes	YES	Vomiting	2 Hrs.	Complete
25	30	Male	Quadriparesis	1/5	Diminished	No	No	Diarrhoea	1 Hrs.	Complete
26	55	Male	Quadriparesis	3/5	Absent	No	No	TPP	7 Hrs.	Complete
27	35	Female	Quadriparesis	2/5	Absent	No	No	Sjogren's Syndrome	3 Hrs.	Complete
28	24	Female	Parapaesis To Quadriparesis	3/5	Diminished	No	No	Unknown	4 Hrs.	Complete
29	46	Male	Paraparesis	3/5	Absent	Yes	No	Diarrhoea	3 Hrs.	Complete
30	36	Female	Paraparesis To Quadriparesis	2/5	Diminished	No	No	Vomiting+ Diarrhoea	2 Hrs.	Complete

Table 4: The Demographics and Clinical Profiles of the Patients in the Study

TPP: Thyrotoxic periodic paralysis.

DISCUSSION: In our study, thyrotoxicosis was present in 40% cases and was the most frequent identifiable cause. The Asian population has a high propensity to develop thyrotoxic periodic paralysis. The most common cause was Graves's disease, although it may occur in association with any of the causes of hyperthyroidism. The high incidence of Thyrotoxicosis Periodic paralysis (TPP) in Asians and the association with the presence of HLA-DRw8 suggests that the basic defect may be genetically determined, but the precise pathogenesis of TPP remains unclear.[4] Familial cases are inherited in an autosomal dominant manner. Mutations in CACNA1S and SCN4A gene adversely affect the function of calcium and sodium ion channels servicing muscle cells, respectively. The KCNJ2 gene codes for inward rectifying potassium channels (Kir 2.1) that moves potassium ions into the cells of skeletal and cardiac muscles. Mutations of this gene have been known to cause familial periodic paralysis with arrhythmias and Andersen-Tawil syndrome.

Increased activity of the Na^+-K^+-ATP-ase pump by thyrotoxicosis induced the hyperadrenergic state, directly by thyroid hormone per se or by hyperinsulinaemia, which leads to increased cellular potassium uptake and hypokalaemia.[5] Female predominance was documented in our study which is against the previous observations.[6,7] The male preponderance in other studies was probably due to excessive exposure to heat and exertion following outward activities. More number of cases were documented in the summer months (63.3%) compared to winter. These findings in our study are consistent with an earlier Indian study, which had also shown high prevalence of cases of hypokalaemic paralysis in the summer season.[8] In our study, we could not find any correlation between severity of hypokalaemia and severity of weakness like several other workers. But, few studies have also observed correlation of severity of weakness and severity of hypokalaemia.[7] Various triggers have been found to be associated with hypokalaemia. Prompt identification of these triggers forms the corner stone for the diagnosis and managements of the cases.

Triggers	Examples	Notes
High glycaemic index foods	Sweetened Drinks, Pasta, Certain Fruits, White Bread, Certain Cereals And Fruits, For Example, Watermelon, Rice, Potatoes	High Glycaemic Index Foods Promote Release of Higher Insulin
Salt/High Sodium Intake	High-salt containing foods	Promotes Diuresis And Loss Of Potassium
Stresses	Infection, Psychological, Surgery	Release of Catecholamines which can activate Na/K/ATPase pump
Ambient Temperature	Cold weather	

Physical Activity	Rest After Significant Exertion	Weakness Maybe Apparent First Thing in the Morning
Gastrointestinal	Diarrhoea	Loss of Potassium
Drugs	Acetazolamide, Oestrogen, Diuretics, Laxatives, Liquorice, Cortisol, Aminoglycosides, Macrolides, Fluoroquinolones	Listed Antibiotics Adversely Affect Neuromuscular Transmission
		Liquorice and Cortisol Promote Potassium Excretion
		Oestrogen Can Increase Insulin Resistance

Table 5: Triggers for Hypokalaemic Paralysis

Diagnosis rests on high degree of suspicion and the work up of the cases should be done on protocol basis to come to a proper aetiological diagnosis which helps in the best management of the cases. Algorithmic approach of the cases helped us to diagnose the rare presentation of hypokalaemic paralysis in cases of MCTD, Sjogren syndrome and Bartter's syndrome which were rarely described in the literature. Bartter syndrome is a group of disorder characterised by hypokalaemic metabolic alkalosis with hypercalciuria and salt wasting. 4 types of Bartter syndrome are present. Type 1, 2, 4 are also called antenatal Bartter syndrome, characterised by maternal polyhydramnios, recurrent salt wasting, severe episodes of recurrent dehydration, type 3 is classic Bartter syndrome, it can be present in adults, milder phenotype. Bartter syndrome occurs due to genetic mutation in renal tubule (Loop of Henle). The genetic defect responsible for classic Bartter syndrome is basolateral chloride channel CLC-Kb. In this, patient's blood pressure is normal, urine calcium is normal in case of type 3 Bartter syndrome. Bartter syndrome commonly present at childhood, very rarely present in adulthood.

Sjogren syndrome is a chronic, slowly progressive autoimmune disease characterised by lymphocytic infiltration of exocrine glands resulting in xerostomia, dry eyes. One third of the patients present with systemic manifestations. Primary Sjogren syndrome patients experience at least one episode of non-erosive arthritis during the course of their disease. Renal involvement includes interstitial nephritis, clinically manifested as hyposthenuria, renal tubular dysfunction with or without acidosis. Untreated acidosis may lead to nephrocalcinosis. Glomerulonephritis is a rare finding that occurs in patients with mixed cryoglobulinaemia or with systemic lupus erythematosus overlapping with Sjogren syndrome. The prevalence of renal involvement in primary Sjogren syndrome is 9%. In our patients, we diagnosed Sjogren syndrome with renal tubular dysfunction without acidosis. In Bloch et al study, they investigated patients retrospectively and found hyposthenuria either transiently or persistently in 10 out of 62 patients, and several case reports suggested severe episodes of hypokalaemic periodic paralysis can occur in Sjogren syndrome.

MCTD is an overlap syndrome that embraces features of SLE, scleroderma, polymyositis/dermatomyositis. Raynaud's phenomenon is the most common and earliest problem. Initially renal involvement was considered as rare. After four decades of trials, renal involvement was thought to be present in about 25%. RTA is a disorder of renal tubule acidification characterised by hyperchloraemic acidosis and hypokalaemia and inability to lower urinary pH <5.5. In this disorder, distal nephron does not lower urinary pH because collecting duct permits back diffusion of H+ ions. Chronic acidosis impairs absorption of calcium causing renal hypercalciuria and mild secondary hyperparathyroidism. Osteomalacia occurs because of acidosis induced loss of bone material and inadequate production of 1, 25 (OH) 2D3, and may present with pseudofractures which occurred in our last case.

Majority of cases of type 1 RTA result from Sjogren syndrome, SLE, scleroderma which are part of mixed connective tissue overlap syndrome. In our patients, serology was positive for ANA, U1RNP, RO-52, SS-B/LA along with, recurrent hypokalaemia, low urinary pH, low serum calcium, fracture femur suggesting recurrent hypokalaemia with osteomalacia secondary distal RTA (Type 1) secondary to MCTD (Serological positive). Correction of potassium levels with the electrocardiographic correlation either by oral route or parenteral route (In severe cases) results in resolution of symptoms in many cases. The patients with thyrotoxic periodic paralysis should be given beta blockers as a part of treatment in order to reverse the transcellular shift of the potassium.[9] Thyroid levels should be corrected. Prompt recognition and correction of the underlying aetiology favours a good prognosis in terms of residual weakness.

CONCLUSION: Hypokalaemic periodic paralysis is a heterogenous group of disorder. A significant number of patients had thyroid disorders mostly in the form of thyrotoxicosis, non-renal and renal loss of potassium like diarrhoea and vomiting. Early recognition and prompt management of these conditions is essential to prevent residual deformity and further attacks in future.

- Recurrent Hypokalaemia + Osteomalacia = RTA.
- Recurrent hypokalaemia + Osteomalacia + High titres of antibodies = Overlap syndromes.
- Recurrent Hypokalaemia + Hypertension = Liddle Syndrome.

Mineralocorticoid Excess.

- Recurrent Hypokalaemia + Age <25 yrs. = Channelopathy.
- Recurrent Hypokalaemia + Hypomagnesaemia = R/o Bartter Syndrome or Gitelman Syndrome.
- Recurrent Hypokalaemia + Fine tremors = Thyrotoxic periodic paralysis.

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