A STUDY OF HYPOKALEMIC PARALYSIS- ETIOLOGY, CLINICAL PROFILE AND OUTCOME

Dissertation submitted to

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for the award of the degree of

DM (NEPHROLOGY) – BRANCH – III

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CHENNAI

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DECLARATION

I solemnly declare that this dissertation titled "**A STUDY OF HYPOKALEMIC PARALYSIS- ETIOLOGY, CLINICAL PROFILE AND OUTCOME**" is done by me in the Department of Nephrology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of Prof.N.Gopalakrishnan, MD., DM., FRCP., Professor & Head of the Department, Department of Nephrology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfillment of the university requirements for the award of the degree of DM.Nephrology.

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CERTIFICATE

This is to certify that the Dissertation entitled, **"A STUDY OF HYPOKALEMIC PARALYSIS- ETIOLOGY, CLINICAL PROFILE AND OUTCOME"** is the bonafide record work done by *Dr.G.Chandramohan*, under our guidance and supervision in the Department of Nephrology, Government General Hospital, Madras Medical College, Chennai, submitted as partial fulfillment for the requirements of D.M. Degree examination Branch III NEPHROLOGY, AUGUST 2011, under The Dr.M.G.R. Medical University, Chennai.

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INTRODUCTION

Acute flaccid paralysis is a potentially reversible medical emergency and has a wide differential diagnosis that includes neurologic, metabolic and infectious etiologies. Acute hypokalemic paralysis (HP) constitutes a group of heterogenous disorders that present with acute muscular weakness and can at times be potentially life threatening[1]. Complications secondary to hypokalemia such as a cardiac arrhythmia or respiratory failure lead to morbidity and mortality. Although there are many potential causes of hypokalemia, there are far fewer entities in the differential diagnosis of hypokalemic paralysis. Hypokalemia and paralysis can be divided into 2 types, hypokalemic periodic paralysis (HPP) where there is short-term shift of potassium into cells and non-HPP resulting from a large deficit of potassium due to various etiologies. The differential diagnosis in a patient with HP can be challenging due to heterogeneity of its etiologies, but it is important to make the diagnosis promptly because different therapies are required for each type and identifying causes that are reversible are important[2]. Presence of a positive family history and recurrent episodes in a patient can be helpful in making a diagnosis of HPP , but HPP and non-HPP are almost indistinguishable and there is diagnostic difficulty[2].

Familial periodic paralysis has been reported as the most common cause of hypokalemic paralysis in Caucasians. Thyrotoxic hypokalemic paralysis (TPP) is common in the Asian (oriental) population. The etiology of

hypokalemic paralysis is likely to depend on ethnicity, vigor of the investigation, and the setting of the medical practice[3].

In this study an attempt has been made to analyze the various etiologies of HP that appears to be common in our region. We have also analyzed the metabolic profile that will aid in diagnosis and outcome of patients with hypokalemic paralysis.

AIM

To analyze the clinical presentation, etiology, and outcome of patients presenting with hypokalemic paralysis.

Review of Literature

Claude Bernard wrote that 'the constancy of the internal milieu is the essential condition to a free and independent life'. Potassium is the most abundant cation in the human body, with total body stores amounting to 50 mmol/kg in adults. Less than 2% of K^+ is located extracellularly, and kalaemia is maintained in the narrow range of 3.5–5.0 mmol/L. Normal individuals ingesting 80–100 mmol of K^+ daily remain in balance by virtue of short-term transcellular K^+ shifts regulated by insulin, aldosterone and β-adrenergic catecholamines (β2 receptors), which increase the cellular K^+ uptake by stimulating the sodium pump (Na^+/K^+-ATPase), and the excretion of 90% of the ingested K^+ in the urine and the remaining in stool.[4]

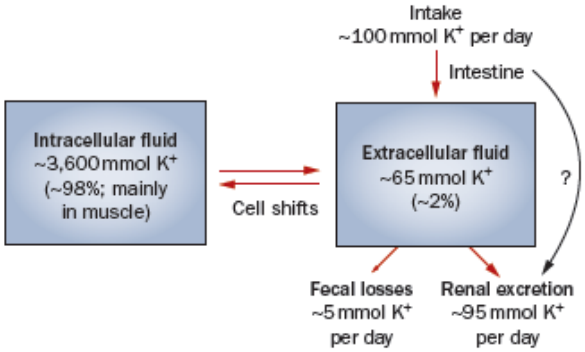


Figure 1 | Distribution of K^+ in the body. Approximately 98% of the body's K^+ is located in the intracellular fluid, mainly in skeletal muscle, and only approximately 2% is located in the extracellular fluid. The pool of K^+ in the extracellular fluid is determined by input from the gastrointestinal system and output in the urine and stools, as well as the distribution between the extracellular fluid and the intracellular fluid compartments. A novel hypothesis is that the gut can somehow signal to the kidneys to excrete K^+ abruptly when sudden gastrointestinal K^+ loads occur. Abbreviation: K^+, potassium.

Fig1[5]

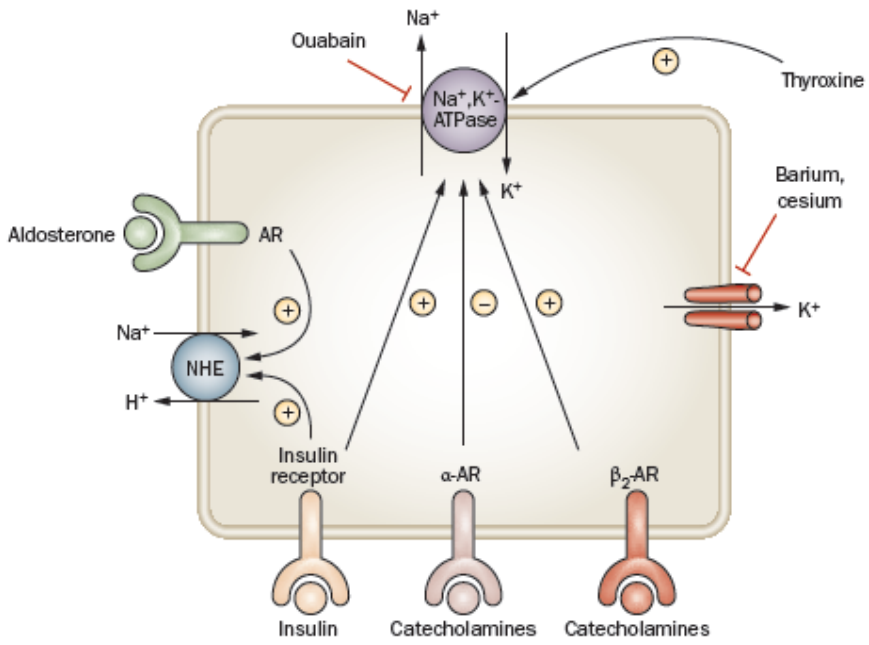


Figure 2 | Cellular shifts in K^+. A simplified diagram showing the important transporters involved in K+ distribution across cell membranes, including the Na^+,K^+-ATPase 'sodium pump', K^+ channels and NHE. Substances that act on these channels and transporters to induce cellular shifts in K^+ are also shown.

Abbreviations: α-AR, α-adrenergic receptor; β_2-AR, β_2-adrenergic receptor; AR, aldosterone receptor; H^+, hydrogen; K^+, potassium; Na^+, sodium; NHE,Na^+/H^+ exchanger.

Fig 2 [5]

Hypokalemia is common in patients who are ill, have a fever or are malnourished, including those with eating disorders, alcoholism or AIDS. Women develop hypokalemia more often than men, especially when given thiazide diuretics; the increased susceptibility of women to hypokalemia is probably related to reduced muscle mass and a smaller pool of exchangeable K^+.[5]

The most prominent clinical features of hypokalemia or potassium depletion are neuromuscular, although other systems, such as cardiovascular and gastrointestinal, may also be affected. Some patients complain of muscular weakness, especially of the lower extremities, while marked and generalized weakness of skeletal muscles is common with more severe potassium depletion. Very severe hypokalaemia may lead to virtually total paralysis including respiratory, bulbar and cranial musculature. Deaths from respiratory failure and arrhythmia have been reported.

Differential diagnosis of hypokalaemic paralysis (modified from ref [6])

Transcellular distribution of K (no depletion)

- Familial periodic paralysis
- Thyrotoxic periodic paralysis
- Barium poisoning

Actual K depletion

Renal loss

- RTAs
- Sjögren's syndrome
- Medullary sponge kidney
- Chronic toluene exposure
- Fanconi's syndrome

- Tubulointerstitial disorder, Gitelman syndrome, Barrter syndrome
- Primary hyperaldosteronism
- Drug-induced: Gentamicin, carbenicillin, amphotericin B, degraded tetracycline, vitamin B_{12}, alcohol, carbenoxolone, overdoses of chloroquine, the antipsychotic agents risperidone or quetiapine[9]
- Others - water intoxication, nephrotic syndrome,diuretic phase of acute tubular necrosis, treatment phase of diabetic ketoacidosis, chlorothiazide-associated hypokalaemia, hypokalaemia following ureterosigmoidostomy , Licorice[6] consumption, Leptospirosis[18], Cleistanthus collinus poisoning.[19]

Extra-renal loss

- Celiac disease
- Tropical sprue
- Acute gastroenteritis
- Short bowel syndrome

Hypokalemic periodic paralysis

Ion channels constitute a class of proteins that is ultimately responsible for generating and orchestrating the electrical signals passing through the thinking brain, the beating heart, and the contracting muscle. Defective ion-channel proteins are responsible for cystic fibrosis, the long-QT syndrome,

heritable hypertension (Liddle's syndrome), familial persistent hyperinsulinemic hypoglycemia of infancy, hereditary nephrolithiasis (Dent's disease), and a variety of hereditary myopathies, including generalized myotonia (Becker's disease), myotonia congenita (Thomsen's disease), periodic paralyses, malignant hyperthermia, and central core storage disease[7] .

The periodic paralyses, paradigm for muscle channelopathies

The periodic paralyses are rare and dominantly inherited disorders characterized by neuromuscular symptoms (paralysis and myotonia) associated with marked and transitory variations of K^+ levels in the plasma [8] . Symptoms usually appear during the first or second decade of life and can be life-threatening if heart or respiratory muscles are involved.

Familial Hypokalemic periodic paralysis

Nomenclature

Hypokalemic periodic paralysis was also known as Cavare-Romberg syndrome, Cavare-Westphal syndrome, Cavare-Romberg-Westphal syndrome, Westphal's disease, Westphal's neurosis . Karl Friedrich Otto Westphal (1833-1890) first described extensively and convincingly the main characteristics of the disease, which had previously been described as "periodic palsy" by Musgrave

in 1727, Cavare in 1853, and Romberg in 1857. Hartwig reported a case of palsy with muscle inexcitability provoked by rest after exercise in 1875. It was not until 1887 that a dominant pedigree was described by Cousot[10].

Ion channels involved [11]

Sodium channel

Hypokalemic PP (HypoPP2)

Calcium channel

Hypokalemic PP (HypoPP1)

Potassium channel

Andersen-Tawil syndrome

(Hyperkalemic PP or hypokalemic PP)

Prevalence [12]

The prevalence of HOKPP is unknown but thought to be approximately 1:100,000. Inheritance is autosomal dominant with reduced penetrance in women. Symptoms begin early in life and rarely after the age of 25 years. Typically affects Caucasians with male preponderance. Male to female ratio is 3:1.2 Age of onset was earlier and the duration of episodes was longer in HypoPP1 (10 years; 20 h) versus HypoPP2 (16 years;1 h).

Genetics and Inheritance [10]

Calcium Channel –

- Voltage-Dependent, L Type,
- Skeletal Muscle Dihydropyridine-Sensitive, Alpha-1 Subunit;
- CACNA1S Gene map locus 1q32
- Seven Mutations described to Date: ARG1239HIS, ARG528HIS , ARG528GLY , ARG1239GLY , ARG1086CYS & ARG1086HIS

Sodium Channel –

- Voltage-Gated, Type IV,
- Alpha Subunit;
- SCN4A; Gene map locus 17q23.1-q25.3
- Six mutations described to date: ARG669HIS , ARG672HIS, ARG672GLY , ARG672SER , DIII-S4 ARG1132Q and alpha subunit, between 4th/5th transmembrane segments, domain III SCN4A, Pro1158Ser.

Potassium channel-

- Inward-rectifying potassium channel Kir2.1
- KCNJ2 gene; Gene map locus 17q24.3;
- More than 20 mutations described

Pathophysiology

The pathophysiology behind the disorder is poorly understood. This is a type of skeletal muscle channelopathy. Several mutations have been reported in skeletal muscle dihydropyridine receptor calcium channel(CACNL1A3), tetrodoxin sensitive voltage sensitive sodium channel(SCN4A) and potassium channel(Kir2.1). However sporadic cases without documented evidence of mutation have been reported[8].

Cav1.1 is the main subunit of the voltage-gated pentameric L type Ca^{2+} channel complex (also called the dihydropyridine receptor) located in the transverse (t) tubular system. Via Cav1.1, a t-tubular action potential activates the Ca^{2+} release channel (also called the ryanodine receptor) and the Ca^{2+}released from the sarcoplasmic reticulum activates the contractile machinery. Hypokalemic PP types 1 and 2 are clinically similar and in both responsible channels, the mutations are located exclusively in the voltage sensing S4 segments: those of SCN4A are situated in domain 2 and those of Cav1.1 in domains 2 or 4. Functionally, the inactivated state is stabilized in the Na^{+} channel mutants, while the channel availability is reduced for the Ca^{2+}channel mutants. It is still unclear how the loss-of-function mutations of these two cation channels can produce the long-lasting and pronounced membrane depolarization that inactivates the sodium channels and thereby leads to the fiber inexcitability[8] .

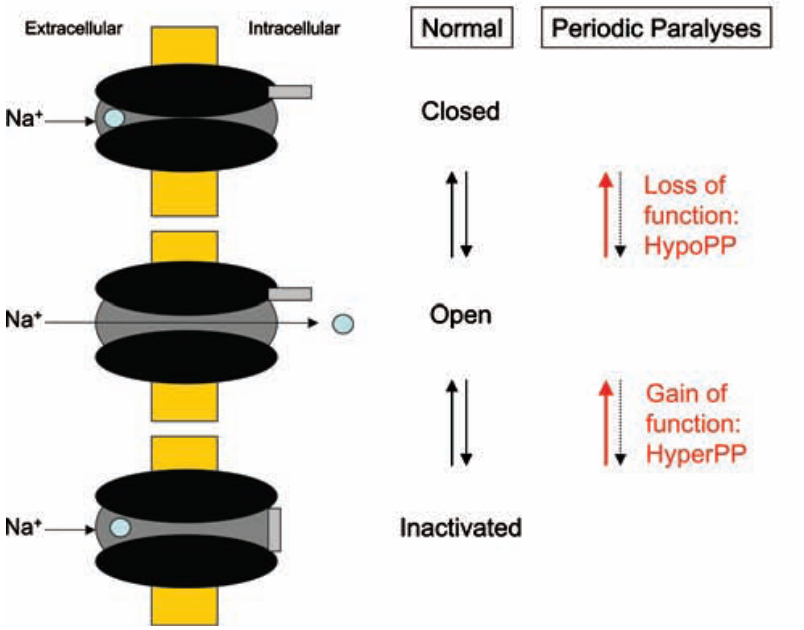


Fig .3 Voltage-gated ion channel function in normal and pathological conditions; physiologically, Na^+ voltage-gated channels switch between three different states (closed, open and inactivated) according to time and membrane potential variations.When the channels are open, there is an inward Na^+ current and a compensatory K^+ outward current (not represented) responsible for the generation and transmission of the action potential. In the case of hyperkalaemic periodic paralysis (HyperPP), mutations affecting the tertiary structure of the protein reduce the affinity of the fast inactivation particle(corresponding to the intracellular protein loops between transmembrane domains III and IV of Nav1.4) for his docking site. In these situations, Nav1.4 channels stay preferentially in their open, activated state (gain-of-function defect) causing a Na^+ inward current, a sustained membrane depolarization and the release of K^+ from muscular cells. By contrast, in the case of hypokalaemic periodic paralysis (HypoPP), mutated channels remain closed after membrane depolarization (loss-of-function defect), causing a lack of action potential initiation/ transmission responsible for muscle inexcitability. [4]

Kir2.1 channels stabilize the resting membrane potential in skeletal and cardiac muscle. Reduced Kir2.1 channel function in skeletal muscle may cause sustained membrane depolarization, leading to failure of action potential propagation and flaccid paralysis[12].

Clinical features and Diagnosis

The attack frequency varies from daily to yearly and attacks frequently lasts for 3 to 4 hours to a day or more and are frequently precipitated by sleep or rest after exercise, alcohol or high carbohydrate meal and almost never occur during exercise. The limb muscles are more affected than the trunk muscles and proximal muscles are more affected than the distal ones.[11] Diagnosis is made by demonstrating the presence of low potassium during a paralytic attack and by excluding other secondary causes of hypokalemia. ECG will show features of hypokalemia. A clinical diagnosis of sporadic periodic paralysis can be made if hyperthyroidism and family history of HPP are both absent[13].

Thyrotoxic periodic paralysis

Epidemiology

Incidence of Thyrotoxic periodic paralysis is highest among Asian population. Approximately 2% of patients in China and Japan reportedlyhave TPP. Despite a higher incidence of thyrotoxicosis in women TPP occurs predominantly in men; the male-female ratio is approximately 20:1. Presence of Certain HLA antigen subtypes such as HLA-DRw8 , A2, Bw22,Aw19 and B17

is suspected to make some of the Asian population susceptible to TPP. TPP occurs most commonly in summer and autumn. Increased consumption of sweet drinks, outdoor activities and exercise and increased potassium loss in sweat are possible explanations for the seasonal pattern[14].

Pathophysiology[15]

- Hyperthyroidism results in hyperadrenergic state. β_2 adrenergic stimulation increases the activity of Na^+,k^+-ATPase pump.
- Thyroid hormone per se increases the activity of Na^+,k^+-ATPase pump.
- Hyperinsulinemia observed in patients with acute attack of TTP indirectly also stimulates Na^+,k^+-ATPase pump.

Clinical & Laboratory findings

Occurs in persons aged 20-40 years in contrast to familial HPP which occurs in persons aged less than 20 years[15]. Nearly half of the patients with TPP have no obvious symptoms related to hyperthyroidism during an attack[17]. Patients usually have abnormal thyroid functions, hypokalemia,with a urinary potassium-creatinine ratio less than 2meq/mmol. Urinary phosphate excretion is reduced remarkably as a result of increased shift of phosphate into the cells . Hypercalciuria and hypophosphaturia need to be emphasized in diagnosing TPP[14].

TPP attacks occur only when thyrotoxicosis is present. Attacks can be induced by insulin and carbohydrate administration in hyperthyroid patients with a history of TPP, but not in TPP patients who have become euthyroid. Paralytic attacks can recur with relapse into a thyrotoxic state, and can be induced by exogenous thyroid hormone.[17]

Barium poisoning

The first cases were referred to as Pa Ping disease, due to an outbreak of paralysis in the Pa Ping area of the Szechwan province of China caused by ingestion of table salt contaminated by a periodic barium salt. Most of the instances of acute toxicity have occurred due to ingestion of barium carbonate (rodenticide), food contaminated by barium carbonate (used in error instead of potato meal), or carelessness in handling rat poison whereby it is mixed with flour and eaten. The fatal dose of barium carbonate is about 0.8 g. However, barium doses as low as 0.2–0.5 mg/kg body weight, resulting from barium carbonate or chloride ingestion, have been found to produce toxicity in adults. A shift of potassium from extracellular to intracellular fluid is the basis of acute hypokalaemia in cases of barium carbonate toxicity. The exact mechanism of hypokalaemia is not known, however, it may be due to the activation of sodium–potassium-stimulated ATPase at the cell surface causing potassium entry into the cell at the cost of extracellular fluid. Barium is reported to block the potassium channels and thereby reduce the potassium efflux from muscles. It also

competitively reduces the permeability of the cell membrane to potassium which may lead to membrane depolarization. The treatment of barium-induced hypokalaemic paralysis has been intravenous potassium administration.The potassium reverses the hypokalaemia as well as displacing barium from potassium channels, allowing it to be excreted in urine. [6]

Renal Tubular Acidosis

Introduction

Renal tubular acidosis (RTA) comprises of a group of disorders characterized by a low capacity for net acid excretion and persistent hyperchloremic metabolic acidosis.

Physiology

The proximal renal tubule is the site of the bulk of solute and water reabsorption in the nephron. Approximately 60% of the filtered sodium (Na^+) is reabsorbed in the proximal segments, along with water, potassium (K^+), bicarbonate (HCO_3^-), phosphate, amino acids and low molecular weight proteins. In contrast, the distal tubule has a specialized role in the final modification of urine concentration and pH. Specialized transporters are involved in the regulation of Na^+ and K^+ reabsorption and H^+ secretion.[20]

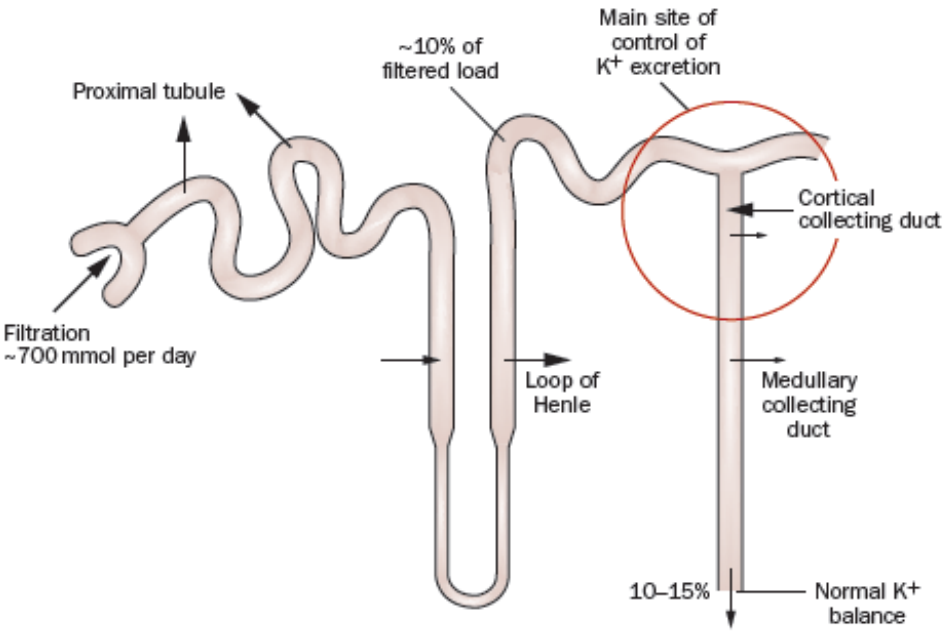


Figure 3 | Renal K^+ handling. Most filtered K^+ is reabsorbed in the proximal tubule and loop of Henle, so that approximately 10% of the filtered load arrives at the distal tubule, regardless of the state of K^+ balance. Control over the amount of K^+ excreted resides mainly in the connecting tubule and cortical collecting duct, where connecting tubule and principal cells secrete K^+ and A-type intercalated cells can reabsorb K^+ (at least during K^+ depletion). Under normal circumstances, the amount of K^+ secreted by the connecting tubule and principal cells determines how much K^+ is excreted in the urine. Abbreviation: K^+, potassium.

Fig 4 . Renal potassium handling [5]

Classification of RTA

Based on pathophysiology, RTA has been classified into three types: type 1 (distal) RTA; type 2 (proximal) RTA; and type 4 RTA secondary to true or apparent hypoaldosteronism. they can be either primary, with or without known genetic defects or secondary to other causes. Secondary RTA is more common than the primary variety. Renal involvement is reported to occur in up to 67% of patients with primary Sjögren's syndrome. [21]

Pathophysiological basis

The primary defect in proximal RTA is reduced renal threshold for HCO^{3-}, resulting in bicarbonaturia. Renal $NaHCO_3$ losses lead to intravascular volume depletion, which in turn activates the renin-angiotensin-aldosterone system. Distal Na^+ delivery is increased as a result of the impaired proximal reabsorption of $NaHCO_3$. Because of the associated hyperaldosteronism and increased distal nephron Na^+ reabsorption, there is increased K^+ secretion. The net result is renal potassium wasting and the development of hypokalemia. In the steady state, when virtually all the filtered HCO_3^- is reabsorbed in the proximal and distal nephron, renal potassium wasting is less and the degree of hypokalemia tends to be mild. Proximal RTA may represent isolated or generalized proximal tubular dysfunction, the latter (Fanconi syndrome) characterized by tubular proteinuria and aminoaciduria and variable degrees of bicarbonaturia, phosphaturia, Na^+ and K^+ wasting and glucosuria[22]. K^+ wasting is enhanced due to increased distal tubular delivery of Na^+ and hyperaldosteronism secondary to volume contraction. Proximal RTA without Fanconi syndrome may be inherited as autosomal dominant and recessive form.

The diagnosis of proximal RTA calls for study of other proximal tubular functions. Proximal RTA should be suspected in a patient with a normal anion gap acidosis and hypokalemia who has an intact ability to acidify the urine to below 5.5 while in a steady state.[23] Proximal tubular dysfunction, such as

euglycemic glycosuria, hypophosphatemia, hypouricemia, and mild proteinuria, helps support this diagnosis. The UAG is greater than zero, indicating the lack of increase in net acid excretion. Disorders that are associated with proximal RTA and Fanconi syndrome should be specifically screened for, including cystinosis, Lowe's syndrome, galactosemia and Wilson's disease[24].

Causes of Type 2 RTA[22]

Not associated with Fanconi syndrome

- Sporadic
- Familial
- Disorders of Carbonic anhydrase
  - Drugs: Acetazolamide, sulfanilamide, topiramate
  - Carbonic anhydrase II deficiency

Associated with Fanconi syndrome

Selective(no systemic disease present)

- Sporadic
- Familial
  - AR proximal RTA with ocular abnormalities
  - AR proximal RTA with osteopetrosis and cerebral calcification

Generalized(systemic disorder present)

- Genetic disorders
  - Cystinosis
  - Wilson’s disease

- Hereditary fructose intolerance
- Lowe syndrome
- Metachromatic leukodystrophy

Dysproteinemic states

- Myeloma kidney
- Light chain deposition disease

Primary and Secondary hyperparathyroidism

Drugs and toxins

- Outdated tetracycline
- Iphosphamide
- Gentamicin
- Lead, Cadmium, Mercury

Tubulointerstitial disease

- Post-tansplant rejection
- Balkan nephropathy
- Medullary cystic disease

Others

- Bone fibroma
- Osteopetrosis
- Paroxysmal Nocturnal Hemoglobinuria

Hypokalemic Distal RTA

Metabolic acidosis secondary to decreased secretion of H^+ ions in the absence of marked decrease in the glomerular filtration rate is characteristic of distal RTA. Patients with distal RTA are unable to excrete ammonium (NH^{4+}) ions in amounts adequate to keep pace with a normal rate of acid production. In hypokalemic distal RTA, urine pH cannot reach maximal acidity (i.e., remains >5.5) despite systemic acidemia indicating low H^+ concentration in the collecting duct. Distal RTA can be caused by either impaired H^+ secretion (secretory defect) or an abnormally permeable distal tubule, resulting in increased backleak of normally secreted H^+ (gradient defect); it may be genetic or acquired[22]. In the secretory defect, the rate of secretion of H^+ is low for the degree of acidosis. Ideally, with a rate defect the ability to maximally acidify the urine should be retained. However, with a severe rate defect, the time spent in tubule lumen may be insufficient for acidification, and there is failure to maximally decrease the urine pH. The defect in secretory distal RTA may be secondary to defective function of H^+ ATPase, H^+/K^+ ATPase, or the Cl^- / HCO_3^- exchanger.

In distal RTA, the titrable acidity and NH^{4+} secretion is low resulting in systemic acidosis. The development of systemic acidosis tends to diminish net proximal fluid reabsorption with an increase in distal delivery, resulting in volume contraction and activation of the renin-aldosterone system. Increased distal Na^+ delivery coupled to increased circulating levels of aldosterone then leads to increased renal K^+ secretion[22]. Incomplete distal RTA is a variant or

milder form of classic distal RTA, in which there is defective tubular H^+ secretion but plasma HCO_3^- levels are normal. Daily net acid excretion is maintained by enhanced ammoniagenesis. Hypercalciuria and hypocitraturia are present, and there is a risk for nephrolithiasis and nephrocalcinosis.[25]

Distal RTA may be a primary disorder, either idiopathic or inherited, but it most commonly occurs in association with a systemic disease, of which one of the most common is Sjögren's syndrome. Hypergammaglobulinemic states as well as drugs and toxins may also cause this disorder. A common cause of acquired distal RTA is glue sniffing. Inhalation of toluene from the fumes of model glue, spray paint, and paint thinners can give rise to hypokalemic normal gap acidosis through multiple mechanisms. First, toluene inhibits collecting duct proton secretion. Second, metabolism of toluene produces the organic acids hippuric and benzoic acid. These are buffered by sodium bicarbonate, resulting in metabolic acidosis and the production of sodium hippurate and sodium benzoate. If plasma volume is normal, these salts are rapidly excreted in the urine, and a non–anion gap metabolic acidosis develops. If plasma volume is decreased, urinary excretion is limited, they accumulate, and an anion gap metabolic acidosis develops.[22]

Causes of Type 1 RTA [22]

Primary

Idiopathic

Familial

Secondary

- Autoimmune disorders
  - Hypergammaglobulinemia
  - Sjogren's syndrome
  - Primary biliary cirrhosis
  - SLE
- Genetic diseases
  - AD type 1 RTA
  - AR
- Drugs and toxins
  - Amphoterecin B
  - Toluene
- Disorders with nephocalcinosis
  - Hyperparathyroidism
  - Vit D intoxication
  - Idiopathic hypercalciuria
- Tubulointerstitial diseases
  - Obstructive uropathy
  - Renal transplantation

In patients with minimal disturbances in blood pH and plasma HCO_3^- concentration, a test of urinary acidification is required. Traditionally, such a test involved oral NH_4Cl administration to induce metabolic acidosis with assessment of the renal response by serial measurement of urine pH. Many patients poorly tolerate NH_4Cl ingestion because of gastric irritation, nausea, and vomiting. An alternative way to test the capacity for distal acidification is to administer furosemide and the mineralocorticoid fludrocortisone

simultaneously.[26] The combination of both increased distal Na^+ delivery and mineralocorticoid effect will stimulate distal H^+ secretion by both an increase in the luminal electronegativity and a direct stimulatory on H^+ secretion. Normal subjects will lower urine pH to values below 5.5 with either maneuver.

Urine pH & Ammonium chloride loading test [27]

Urine pH is useful for assessing the overall integrity of distal urinary acidification. In the presence of systemic acidosis, present spontaneously or induced by ammonium chloride load, the urine pH is normally <5.5. Presence of urine pH >5.5 during metabolic acidosis suggests defective distal secretion of H^+. It should however be appreciated that the urine pH measures the concentration of free H^+ in the urine. This constitutes <1% of the total amount of H^+ secreted in the distal nephron during systemic acidosis, since most protons are excreted as NH_4^+ or titrable acidity. Urine pH values < 5.5 are seen in subjects with proximal RTA during systemic acidosis and low filtered load (plasma HCO_3^- <15 mEq/L), or in patients with selective aldosterone deficiency.

If systemic acidosis is absent, an oral ammonium chloride challenge (0.1 g/Kg) might be given, followed by the measurement of urine pH every hr for the next 28 hr. If the plasma total CO_2 content falls by 3-5 mEq/L, the urine pH should fall to <5.5. Another protocol involves giving the same dose of ammonium chloride daily for 3-5 days, followed by measurement of urine pH and urinary NH_4^+ excretion; the latter should increase 35 times the baseline by

the third day of induced acidosis. In patients with liver disease, calcium chloride may be used as an acidifying agent at a dose of 2 mEq/Kg. The pH is measured electrometrically on fresh voided, early morning urine specimen. The use of dipstick is not recommended. Urine kept standing is likely to get contaminated or infected with urea-splitting organisms, resulting in high urine pH. The urine pH must be evaluated in conjunction with the urinary NH_4^+ content to assess the acidification process. Low urine pH does not always imply an intact urinary acidification mechanism, if excretion of NH_4^+ is low, as might occur in proximal RTA.

Bartter Syndrome

Introduction

Bartter syndrome is a heterogeneous group of disorders characterized by primary renal tubular disorders associated with hypokalemic metabolic alkalosis and hyperreninemia with normotension. Bartter syndrome is rare and is manifested in childhood or in the perinatal period with severe hypokalemia, metabolic alkalosis, and low-normal blood pressure, all of which are caused by tubular wasting of Na^+ and Cl^-. In contrast, Gitelman's syndrome is mostly a disorder of adults, and hypomagnesemia is a defining feature[22].

Bartter's syndrome may result from mutations affecting any of the four ion transport proteins in the TAL. The proteins affected include the apical loop-

diuretic sensitive sodium-potassium-chloride co-transporter NKCC2 (type 1), the apical potassium channel ROMK (type 2), and the basolateral chloride channel ClC-Kb (type 3). Bartter type 4 results from mutations in barttin, an essential subunit of ClC-Ka and ClC-Kb that enables transport of the chloride channels to the cell surface. The TAL transporters function in an integrated manner to maintain both the electrical potential difference and sodium gradient between the lumen and the cell. Loss of the lumen-positive electrical transport potential that normally drives the paracellular reabsorption of sodium, calcium, and magnesium causes NaCl wasting, hypercalciuria, and mild hypomagnesemia. The clinical syndrome mimics a state induced by chronic ingestion of a loop diuretic. Bartter syndrome from mutations in NKCC2, ROMK, or barttin has a more severe phenotype than that caused by mutations of ClC-Kb. The more severe phenotype typically presents in the perinatal period and is called antenatal Bartter syndrome. The milder variety is called classic Bartter syndrome(Type 3)[22].

In some cases prenatal diagnosis is possible in the presence of important signs and symptoms such as polyhydramnios, polyuria and dehydration. In other patients diagnosis is usually made during childhood due to the appearance of tetanic crises or growth failure. Other patients are completely asymptomatic and the diagnosis is made in adolescent or adult life following blood tests prescribed for intercurrent diseases.

Bartter's syndrome –Types [23]

Type	Inheritance	Locus	Gene	Protein	Renal Abnormalities
Type 1	AR	15q15	*SLC12A1*	NKCC2	Salt wasting; hypokalemia
Type 2	AR	11q24	*KCNJ1*	ROMK	Salt wasting; hypokalemia
Type 3	AR	1p36	*ClCNKb*	CLCNKB	Salt wasting; hypokalemia
Type 4	AR	1p31	*BSND*	Barttin	Salt wasting; hypokalemia

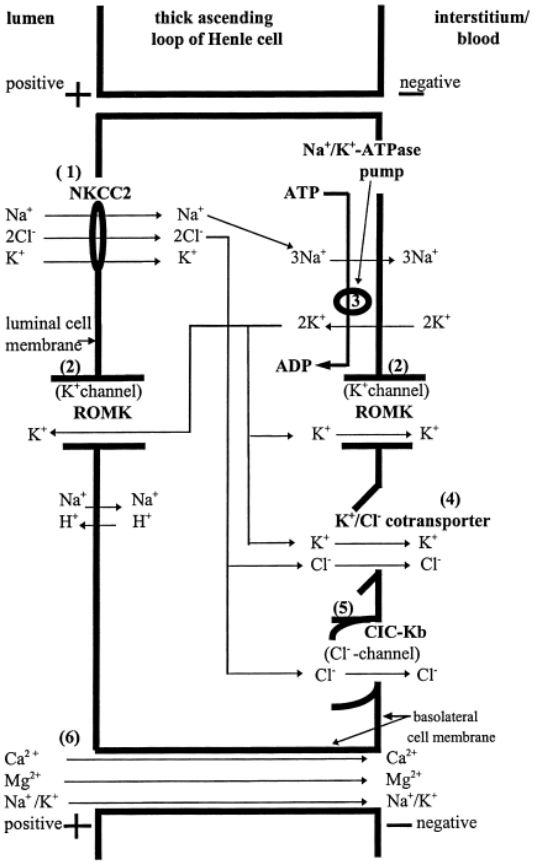


Figure 1. Transport sites in the thick ascending limb of the loop of Henle. (1) Electroneutral $Na^+,K^+,2Cl^-$ cotransport in the apical membrane. (2) K^+ channel (Rat outer medulla potassium channel) in the apical and the basolateral cell membrane. (3) Na^+/K^+-ATPase pump in the basolateral cell membrane. (4) K^+/Cl^- cotransporter in the basolateral cell membrane. (5) Cl^- channel (ClC-Kb) in the basolateral cell membrane. (6) Intercellular space.

Fig 6 : Bartter's Syndrome [23]

Neonatal Bartter's syndrome

Features of neonatal Bartter's syndrome include marked polyhydramnios, premature delivery, weight loss, lethargy, failure to thrive and polyuria[28]. An important biochemical abnormality of the amniotic fluid is consistently elevated chloride levels. In the first week of life, laboratory investigation shows a metabolic alkalosis associated with hypokalaemia. The urine has low specific gravity with very high sodium, chloride and calcium levels, while potassium is normal. However, after 1–3 weeks, the level of potassium in the urine rises to considerably above normal, with relatively less sodium than in the first week of life. Prostaglandin levels are high, both in blood and in urine[29].

Molecular basis

A genetic heterogeneity was clearly demonstrated by Simon et al in those with the antenatal (hypercalciuric) variant of Bartter syndrome, also termed hyper prostaglandin E syndrome . The hypothesis that a loss of function of the absorptive form of the bumetanide-sensitive Na-K-2Cl reabsorption of this segment could produce the features of these patients was proved by Simon et al who demonstrated that the human NKCC2 gene maps on chromosome 15q15-21, is encoded by 26 exons, like TSC, and is made up of 1,099 amino acids. The same group subsequently showed that mutations in another gene encoding the inwardly-rectifying renal potassium channel (ROMK) may also cause the

hypercalciuric variant of Bartter syndrome. This last gene was mapped on chromosome 11q21-25[30,31].

Defects in either Na^+-K^+-$2Cl^-$ cotransport or K^+ channels will result in malreabsorption of Na^+, K^+, Cl^-, and Ca^{2+} in the thick ascending limb of loop of Henle primarily, with subsequent reabsorption of H_2O in the descending loop of Henle. The result of such a defect will be the delivery of large volumes of urine with a high content of Na^+, K^+, Cl^-, and Ca^{2+} to the distal tubule. In the distal tubule, part of the delivered Na^+ will be reabsorbed in exchange for intracellular K^+. By this action, partial but incomplete concentration of the intraluminal fluid will be accomplished, while more potassium wasting becomes evident. However, this impaired sodium absorption in the thick ascending limb of loop of Henle will result in increased levels of prostaglandin E2. This interrelation has been documented in normal individuals using loop diuretics[32].

Increased prostaglandin E2 levels will exacerbate the primary defect of chloride transport in the thick ascending loop of Henle which will[28]:

(i) stimulate the renin-angiotensin- aldosterone axis causing hypokalemia due to increased aldosterone activity;

(ii) impede ROMK channel activity and hence decrease NaCl transport; and

(iii) impede H_2O reabsorption in the collecting ducts due to a secondary effect on vasopressin activity, resulting in hyposthenuria.

Classic Bartter Syndrome

(Bartter syndrome type 3)

Classical Bartter syndrome is characterized by early childhood onset. The patients fail to thrive but have no tetany. Symptoms may include polyuria, polydipsia, vomiting, constipation, salt craving, and a tendency to dehydration. Failure to thrive and growth retardation follows if treatment is not initiated. However the normal adult height usually achieved by untreated individuals is due to a delayed adolescent growth spurt. They have hypokalaemic metabolic alkalosis and their urinary Ca^{2+} is either normal or slightly elevated, with the urine concentration being almost normal. There are reports of Bartter syndrome presenting with hypokalemic periodic paralysis.

Molecular Basis

The biochemical abnormalities of classical Bartter syndrome are all suggestive of a defect related to Cl^- transport in the medullary thick ascending loop of Henle. However, the precise pathway involved is not yet clear. The familial cases of classical Bartter syndrome are inherited as an autosomal recessive entity. A group of patients with this phenotype all had either a large deletion or nonsense, missense, or splice mutations of the gene (CIC-Kb, chromosome 1p36) encoding the renal chloride channels of the basolateral cell membrane.

However, in some patients with classical Bartter syndrome, no abnormality in this gene could be identified. It has therefore been suggested that NaCl transport in the ascending loop of Henle (and the relevant gene/s) may also be involved[28].

Gitelman's syndrome

Gitelman's syndrome is due to mutations in the thiazide-sensitive Na-Cl co-transporter (NCCT) in the DCT. Defects in NCCT in Gitelman's syndrome impair sodium and chloride reabsorption in the DCT and, thus, resemble the effects of thiazide diuretics.

Onset is late, usually after the age of 20 years. Patients present with fatigue, muscle weakness and recurrent episodes of tetany[33] Biochemically, there is metabolic alkalosis, (serum bicarbonate >29 meq/1) profound hypokalaemia, (serum potassium <3 meq/l; normal >3.5 meq/1) hypomagnesaemia (serum magnesium <0.5 meq/l; normal 0.8–1.0 meq/1) and hypocalciuria, (urinary calcium <2 mg/kg per day).[35] Urinary concentrating ability in this disease is mildly impaired.

Pathophysiology

The basic pathology in this disease is an impaired Na-Cl cotransporter in the distal nephron. Distal tubule and collecting duct together reabsorb about 12% of the filtered Na^+. The early distal tubule, also called the cortical diluting

segment, is the site of absorption of NaCl by Na^+-Cl^- cotransport (NCCT) and is the site of action of thiazide diuretics. A similar biochemical abnormality can be seen in long-term use of thiazide diuretics in an otherwise normal individual. NaCl wasting in this part of the distal nephron will lead to mild hypovolemia, and stimulation of the renin- angiotensin axis. Simon et al. showed that there is a complete linkage of Gitelman's syndrome to the locus encoding the renal thiazide sensitive Na^+- Cl^- cotransporter on chromosome 16q13, with an autosomal recessive pattern and a 99% penetrance. Mutant alleles in this disease have been reported by Simon and others. [28]

The late distal tubule and collecting duct have two kinds of cells, each with special feature and function. Principal cells reabsorb Na^+ and H2O and secrete K^+ . Aldosterone acts on principal cells to increase Na^+ reabsorption and increase K^+ secretion. Intercalated cells secrete H^+ ions in exchange for reabsorption of K^+ ions. Aldosterone increases H^+ ion secretion by intercalated cells. Impairment of Na^+-Cl^- cotransport in the early part of the distal tubule results in excessive amounts of Na^+ ion in the late distal tubule. Maximal reabsorption of Na^+ and H2O and maximal secretion of K^+ ion by the principal cells takes place in this segment.At the same time, H^+ is excreted by intercalated cells and this, together with impaired Cl^- reabsorption in the early distal tubule, results in metabolic alkalosis.

The high intake of Ca^{2+} in distal tubule and hence hypocalciuria is probably due to

(a) decreased apical Na+ uptake driving basolateral Na^{+}/ Ca^{2+} exchange with subsequent increase of Ca^{2+} uptake at the apical membrane level and

(b) decreased intracellular Cl- content increasing the polarity of the apical cell membrane, which stimulates Ca^{2+}uptake.[34]

Hypomagnesaemia in Gitleman syndrome is perhaps due to magnesium wasting in distal convoluted tubules of the nephron due to inhibition of Mg^{2+} uptake in the presence of hypokalaemia.[35] It has also been suggested that the metabolic alkalosis may be an important cause of hypomagnesaemia by increasing the resistance of distal tubular cells to Mg^{2+} uptake.[40] With low Mg^{2+} levels in the blood, magnesium wasting has been observed in patients with Gitelman's syndrome, indicating a too-low renal Mg^{2+} threshold.

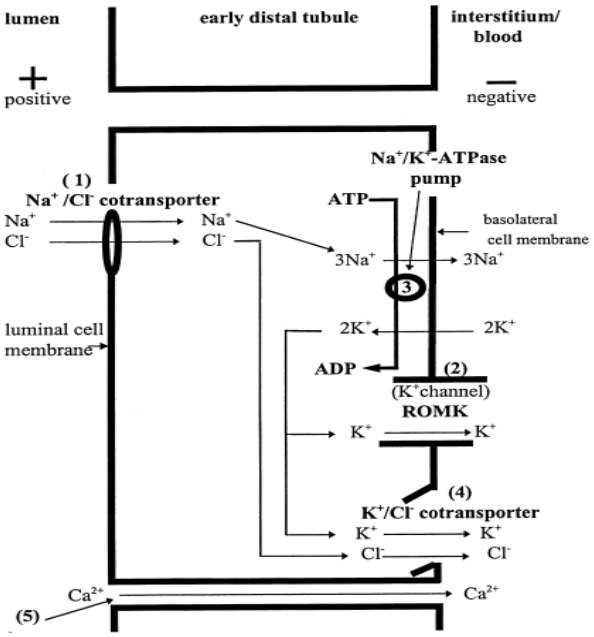


Figure 2. Transport sites in the early distal tubule. (1) Electroneutral Na^+, Cl^- cotransport in the apical membrane. (2) K^+ channel (Rat outer medulla potassium channel) in the apical and the basolateral cell membrane. (3) Na^+/K^+-ATPase pump in the basolateral cell membrane. (4) K^+/Cl^- cotransporter in the basolateral cell membrane. (5) Intercellular space.

Fig 7 . Gitelman's syndrome [23]

Liddle's syndrome

Liddle syndrome is an autosomal dominant syndrome of hypertension and variable degrees of hypokalemic metabolic alkalosis. The patients resemble those with primary hyperaldosteronism, but levels of mineralocorticoid hormones are not increased. Renin and aldosterone are suppressed, and there is no response to spironolactone. However, triamterene and amiloride, aldosterone-

independent inhibitors of distal Na^+ transport, correct hypertension, renal K^+ loss, and hypokalemia.[52]

Pathophysiology

Liddle syndrome is related to mutations of the β or γ subunit of the collecting duct sodium channel ENaC. In Liddle syndrome, the mutated ENaC protein cannot be recognized by NEDD4, a ubiquitin ligase protein; hence, the channels remain in the cell membrane for prolonged periods. This action results in enhanced sodium reabsorption, hypertension, and hypokalemic alkalosis.[53]

Primary Hyperaldosteronism

Primary hyperaldosteronism accounted for about 42% of patients with periodic paralysis in a case series from south India[36]. It is suspected in a patient with hypokalemic periodic paralysis if there is a combination of metabolic alkalosis and hypertension. It is then confirmed by imaging studies and biochemical investigations. Periodic paralysis as a presentation of primary hyperaldosteronism is commonly reported among the oriental races. In a series of 50 patients with primary hyperaldosteronism from Taiwan, 42% presented with periodic paralysis, although all 50 had hypokalaemia[37].

Approach to the patient with hypokalemic palaysis

Failure to distinguish HPP from non-HPP may lead to overly aggressive treatment of an apparent potassium deficit, with rebound hyperkalemia on recovery. In retrospective studies by Manoukain and Lin and colleagues, rebound hyperkalemia occurred in 30% to 42% of patients with HPP, especially if more than 90 mmol of potassium chloride was given within 24 hours[14]. Hence diagnosis of the etiology is important.

Diagnosis for the cause of hypokalemia is based mainly on determining if there is a net loss of K^+ or only a transcellular shift.

Diagnostic tests

Serum K^+

Blood urea nitrogen,

Serum creatinine

Acid-base status

Urinary Potassium

Transtubular potassium concentration gradient (TTKG) and

Urinary Potassium creatinine ratio (K^+/C)

Thyroid function tests – if features suggestive of a transcellular shift

Three urinary indices of renal response to hypokalemia can be easily measured: spot urine potassium concentration, TTKG, and Urine potassium-creatinine ratio.[2]

The spot urine potassium concentration is lower in the HPP than the non-HPP (<15-20 mmol/L); however, there can overlapping values because polyuria is common in patients with hypokalemia . The polyuria may be due to thirst or defective renal concentration in patients with chronic hypokalemia; this leads to a low value for the urine potassium concentration even if significant renal potassium wasting is present.

The TTKG is a semiquantitative index for events in the lumen of the cortical collecting ducts, because it adjusts for the plasma potassium concentration and for water reabsorption in the medullary collecting ducts.[11,18] Although calculating the TTKG is a reliable way to distinguish between HPP and non-HPP, a TTKG is invalid if theUosm is lower than the Posm in a patient.

The potassium- creatinine ratio is independent of the Uosm. Urine potassium-creatinine ratio less than 2.5 mmol/mmol and TTKGs less than 3.0 in hyperosmolar urine are reliable cutoff values to differentiate between patients with HPP and non-HPP.[2]

Fig 8: Appoach to a patient with hypokalemia and paralysis [2]

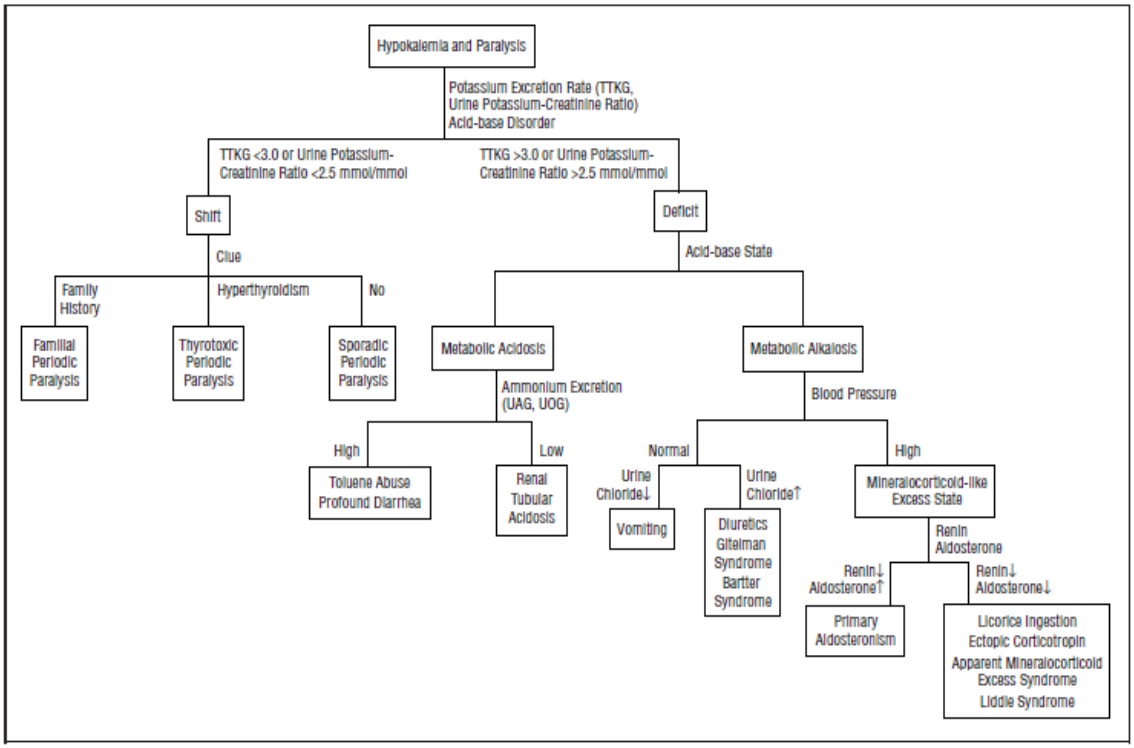


Figure 4. Algorithm for an approach to patients with hypokalemia and paralysis in the emergency department. UAG indicates urine anion gap (sodium+potassium−chloride); UOG, urine osmolar gap ([measured−calculated] osmolality/2); and TTKG, transtubular potassium concentration gradient.

Clinical features suggestive of a transcellular shift :

1. Familial hypokalaemic PP

Caucasian

Family history +ve

Onset in 1st/2nd decade

Precipitated by meals high in carbohydrates/Na^+ or rest/sleep after exercise

Normal acid-base balance , Normal Blood pressure

Low K^+ excretion

2. Thyrotoxic PP

Asian

Family history –ve

Onset in 2nd/4th decade

Sign/symptoms of hyperthyroidism

Predominantly males

Normal acid-base balance, Normal Blood pressure

Low K^+ excretion

Hypokalemia secondary to K^+ loss

Hypokalemia secondary to K^+ loss can be differentiated based on clinical features like Blood pressure and also history suggestive of the aetiologies mentioned below and also by looking at the acid base status and urinary K^+ loss in the patient.

Determination of the urinary K^+ concentration alone might be misleading, because K^+ depletion can cause polyuria and a relatively low K^+ concentration(<20mmol/l) could still represent substantial urinary K^+ loss. The TTKG provides a better way to evaluate the excretory process. [13]

The transtubular K^+ concentration ($[K^+]$) gradient (TTKG) is calculated using the following formula:

TTKG = [urine K^+/plasma K^+] / [urine osmolality/plasma osmolality]

To differentiate individual causes of renal K^+ wasting the following investigations may be done

Urinary pH

Ammonium loading test

Serum and urinary electrolytes – Na , K, Cl, Ca, Phosphate,Mg

Alkaline phosphatase

Creatine kinase

24 h urinary calcium, inorganic phosphate, and creatinine

Urinary aminoacids

Seum aldosterone and renin levels

Management

Treatment of Periodic paralyses

Body potassium stores are normal in patients with FPP and TPP. Hence the aim of potassium supplementation is to normalize the plasma potassium instead of repairing the potassium deficit. Initial treatment of acute episodes of FPP is oral potassium supplementation (0.2-0.4mmol/kg) every 15 to 30

minutes depending on potassium levels, ECG changes and muscle strength. Intravenous therapy is necessary when the patients are unable to swallow or vomiting. Prophylaxis against recurrent episodes has been successful with wide variety of drugs like acetazolamide (125-1000mg/day), spiranolactone (25-100 mg/day) and triamterine (25-100 mg/day).[6]

In a study conducted by Lin et al, they found that the average recovery time is two times shorter in patients with TPP treated with intravenous potassium chloride supplementation at a rate of 10meq/h than in controls. However rebound hyperkalemia occurred in 70% of patients treated with potassium chloride. Patients receiving 50 mmols or less rarely developed hyperkalemia. It appears that low doses may be efficacious while substantially reducing the risk of hyperkalemia[8]. Oral β blockers (propranolol 3-4mg/kg) appear to be effective with out causing rebound hyperkalemia.

Propranolol is effective in preventing recurrent attacks by suppressing the activity of Na^+,k^+-ATPase pump[15]. Regular potassium chloride supplementation is futile because potassium levels are normal during the inter attack period. Acetazolamide can precipitate recurrent attacks of TPP and should not be used[8].

Management of Hypokalemia secondary to potassium loss

Any depletion of potassium – renal or non renal has to be corrected by replacing the lost potassium and also the underlying cause corrected to prevent futher loss.

Treatment of Proximal RTA

Children should treated to prevent growth retardation. Alkali must be given in large amounts daily, 5 to 15 mmol/kg/day, because bicarbonate is rapidly excreted in urine. A thiazide diuretic can be used in conjunction with low salt to reduce the amount of bicarbonate required. Potassium requirements increase during alkali therapy due to increased renal loss of potassium from bicarbonaturia[38].

Adults with proximal RTA are frequently not treated as aggressively as children are because of the lack of systemic metabolic abnormalities or bone disease.[22]

Treatment of Distal RTA

Distal RTA is treated with potassium replacement and alkali solution. The dose is 0.5 to 2 mmol/kg/day with an aim to keep the bicarbonate level above 18mEq/L. Alkali supplementation is either as sodium bicarbonate or Shohl's solution[38] . It is a mixture of 98 gm of hydrated sodium citrate and 140 gm of citric acid dissolved in 1000ml of distilled water. Potassium citrate can be used instead of sodium citrate if hypokalemia correction is required . In patients with osteomalacia, calcium and vitamin D form integral part of therapy in addition to correction of acidosis .

Treatment of Bartter syndrome

The therapeutic management of Bartter syndrome is composed of two major aspects:

(i) replacement therapy and (ii) use of drugs.

Dietary intake of sodium and potassium should be liberal. Potassium supplements are usually required.. Nonsteroidal anti-inflammatory drugs (NSAIDs) are useful, particularly in patients with antenatal Bartter's syndrome, since they reduce prostaglandin production. Indomethacin (1 to 3 mg/kg per 24 hours) [39] or ibuprofen is commonly used for both all types and initial response in good in both types although better in antenatal Bartter.

If not treated, patients may succumb to episodes of dehydration, electrolyte disturbance, or intercurrent infection. With appropriate therapy, most children improve clinically and show catch-up growth; pubertal and mental developments are usually normal. Lifelong therapy is needed. Chronic tubulointerstitial nephropathy due to persistent hypokalemia, hypercalciuria, and nephrocalcinosis may lead to progressive decline in renal function[22].

Treatment of Gitelman's syndrome

Replacement therapy is the main treatment for Gitelman's syndrome, which means magnesium supplementation throughout life. Administration of magnesium in the form of $MgCl_2$ partially corrects hypomagnesaemia and hence prevents the appearance of tetany as well as compensating for ongoing chloride losses by the kidney.[40] Acid-base status, urinary Ca excretion and renin-angiotensin axis are all corrected. Also correction of hypokalemia may

occasionally require the addition of potassium salts and/or anti-aldosterone drugs such as spironolactone or amiloride.[41]

Treatment of Liddle's syndrome

Therapy consists of sodium restriction and K^+ supplements. Triamterene directly inhibits apical Na^+ channels, resulting in increased urinary Na^+ and decreased K^+ excretion and resolution of hypertension. Amiloride also normalizes the blood pressure and K^+ levels. However, most patients continue to have growth retardation. Because the pathogenetic disorder is not correctable with age, lifelong therapy is required.[5]

MATERIALS AND METHODS

Study population

Patients admitted in medical and general wards of Rajiv Gandhi Government General Hospital, Chennai-3, from January 2009- March 2011 with acute onset of flaccid weakness and documented serum potassium of < 3.5 mEq/l during the episode were included in the study. Patients with renal failure (serum creatinine >1.5 mg/dl) were excluded.

Evaluation

Clinical data collected included Age, Sex, ethnic origin, history regarding the evolution of the symptoms, precipitating factors like, high carbohydrate intake in the preceding 24 Hrs, alcohol consumption and treatment taken. Any history of similar disease in the family was enquired about, and reports of weakness, thyroid disease, diarrhea, vomiting, hypertension, bone pain, fractures, dry mouth, dry eyes, and kidney disease were recorded. Intake of drugs like diuretics, β2 agonists, decongestants, insulin, laxatives and antipsychotics were noted. Excessive caffeine and herbal drugs usage were excluded.

The examination included anthropometry, pulse, blood pressure, anemia, thyroid status. Complete neurological examination was performed. Schirmer's test was performed in selected patients.

Laboratory investigations

All patients underwent:

Routine urine analysis

Haemogram,

Blood urea, serum creatinine, serum electrolytes

Serum calcium, inorganic phosphorus

Serum magnesium

Serum albumin,globulin, alkaline phosphatase, creatine kinase

Spot urine potassium, urine chloride

Spot urine potassium, creatinine ratio

Arterial blood gas analysis

Electrocardiogram

Thyroid Function Tests

Ultrasonogram Abdomen.

Early morning urinary pH

Patients with urinary K+ loss and hyperchloraemic metabolic acidosis with normal anion gap underwent:

Lip biopsy

SSA,SSB antibody

ANA

Urinary aminoacids.

Urine Bence Jones Protein, serum electrophoresis.

Patients with urinary K+ loss and metabolic alkalosis underwent:

24 hrs urinary calcium

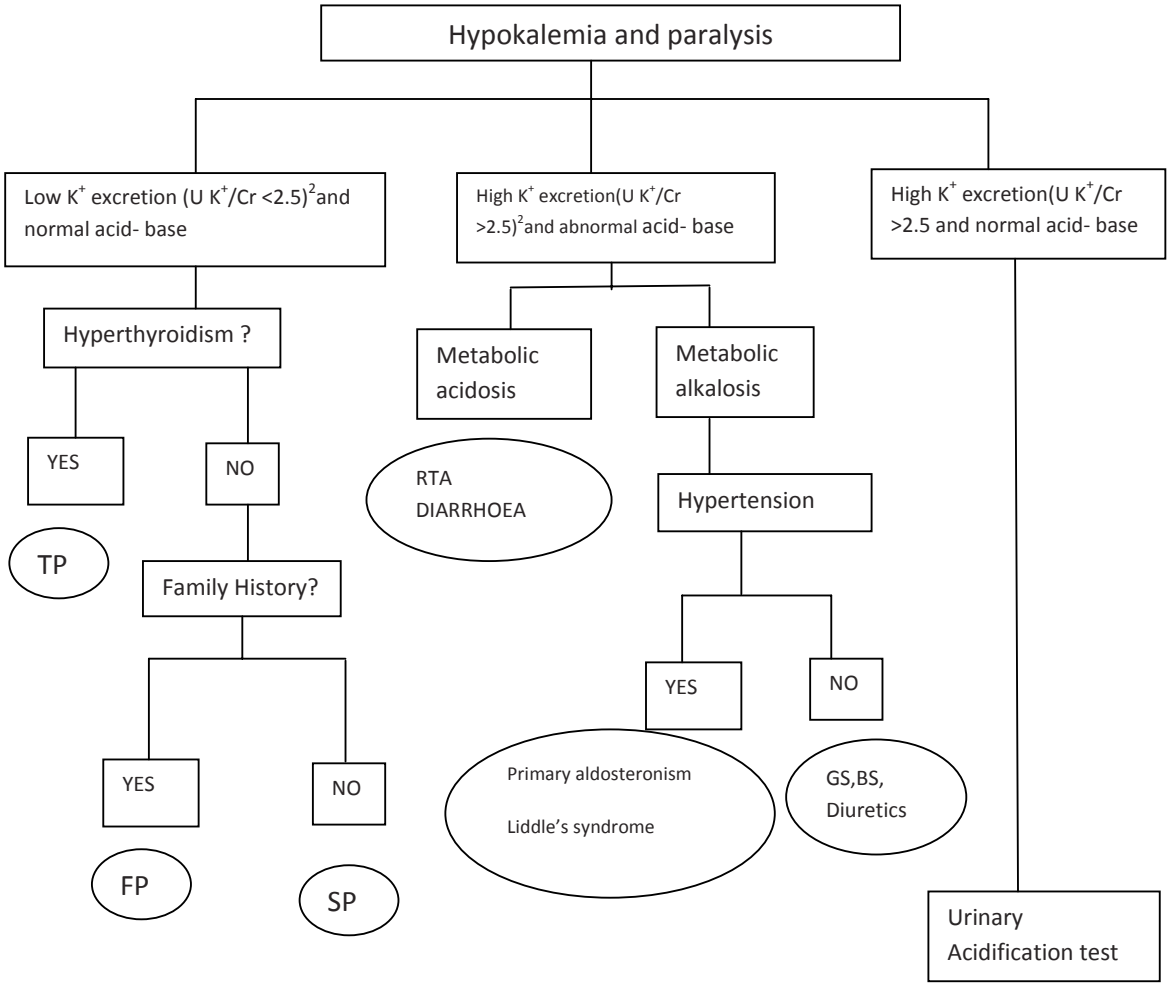
Patients with Urinary K+ loss with normal acid base status underwent an ammonium chloride loading test (0.1 g/kg). TTKG was done when there was doubt in diagnosis of hypokalemia due to transcellular shifts or due to renal loss.

Serum aldosterone, plasma renin levels, and CT scan of the abdomen was done in patients presenting with hypertension, hypokalemia and alkalosis to rule out primary hyperaldosteronism.

Statistical analysis

All data are expressed as mean ± SD. Differences in group means were compared using one-way analysis of variance (ANOVA). Differences in categorical variables were compared using Fisher's exact test. The difference was considered significant if p-value was > 0.05. Data was analyzed using SPSS (V: 17) software.

Diagnostic approach in a patient with Hypokalemic Paralysis (Lin 2001)[14]



RESULTS AND OBSERVATION

This study was conducted between January 2009 and March 2011.There were 47 patients with a mean age of 32.04 years (Range 18- 50 Years). The M:F ratio was 28:19.

Age Distribution

Age	No	%
<25	4	9%
25-34	20	43%
35-44	12	25%
>45	11	23%
Total	47	100%

Hypokalemic paralysis is grouped based on acid-base status into three main groups as shown below.

Groups based on Acid-base status

	No	%
Normal Acid-base	24	51%
Metabolic Acidosis	16	34%
Metabolic Alkalosis	7	15%
Total	47	100%

Out of 47 patients 24(51%) had normal acid base balance, 16 patients (34%) had metabolic acidosis, 6 patients (15%) had metabolic alkalosis.

Sub groups of Hypokalemic paralysis

Sub groups	NO	%
SPP	20	43%
TPP	4	9%
d RTA	15	31%
p RTA	1	2%
GITELMAN'S SYNDROME	6	13%
LIDDLE'S SYNDROME	1	2%

SPP : Sporadic periodic paralysis
TPP : Thyrotoxic periodic paralysis
d RTA : Distal Renal Tubular Acidosis
p RTA : Proximal Renal Tubular Acidosis

Of the 24 patients with normal acid base balance none had evidence of renal potassium loss (Urine potassium creatinine ratio <2.5), 4(9%) patients in this group had biochemical evidence of thyrotoxicosis and were diagnosed as Thyrotoxic periodic paralysis (TPP), and 20(43%) patients who had normal thyroid profile and negative family history of periodic paralysis were diagnosed as Sporadic periodic paralysis (SPP).

Of the 16 patients who had metabolic acidosis, all of them had evidence of renal potassium loss. One patient had features of generalized proximal tubular dysfunction and urine pH was < 5.5 during acidemia and was diagnosed as proximal renal tubular acidosis (p RTA), fifteen patients (31%) had urine pH > 5.5 during acidemia and were diagnosed distal renal tubular acidosis (d RTA).

Seven patients had metabolic alkalosis with renal potassium wasting. Diuretic use was excluded by careful scrutiny. Of them 6 (13%) were diagnosed to have Gitelman's syndrome since they had hypocalciuria and

hypomagnesemia. One patient had hypertension, low plasma renin activity was diagnosed Liddle's syndrome.

Age distribution, gender distribution, mean serum potassium, bicarbonate, pH, serum chloride, urinary K^+, urinary K^+/Cr ratio, Urinary Cl^-, and other clinical characteristics are shown in the table.

Comparing the groups

	SPP	TPP	d RTA	p RTA	GS	LIDDLE	P*
No. of Pts	20	4	15	1	6	1	
M:F	15:5	3:1	4:11	0:1	5:1	1:0	
Age of onset (yrs)	24.6±5.7	43±8.8	36.8±7.3	50	34.67±3.1	32	<0.01
Duration of illness (mo)	22.7±5.07	6.5±4.95	15.4±12	24	37.5±6.3	3	<0.01
No. of episodes	2.9±2	1.5±0.5	3.3±1.7	3	1.5±.57	3	<0.01
Serum K^+(mmols/l)	2.47±0.47	2.8±0.34	2.52±0.49	2.6	2.63±0.43	1.8	NS
Serum Cl^-(mmols/l)	105±13.5	105±5.3	112±6.9	102	97.83±5.8	103	0.042
Urine K^+ (mmols/l)	11.44±2.3	14.75±1.9	28.22±6.7	23	30.91±7	28	<0.01
U K^+/Cr	1.73±0.36	2.07±0.29	4.35±0.8	3.9	5.5±1.3	5.2	<0.01
Time to Improve(hr)	22.7±5.07	23.75±4.4	31.3±6.2	24	37.5±6.3	12	<0.01
Resp paralysis	3	0	2	0	0	0	
Recurrence	4	0	0	0	1	0	
KCl requirement for recovery mmols	58±23	47.5±20.6	101.3±18.8	80	90±17.8	50	<0.01
Rebound Hyperkalemia	2	1	0	0	0	0	

*One-way Analysis of Variance (ANOVA) with Bonferroni Multiple Comparisons Test. (Liddle's syndrome and p RTA excluded)

There is a statistically significant difference in the mean age of onset, the lowest being SPP group followed by Gitelman's syndrome group, d RTA, and then by TPP. Serum chloride is highest in d RTA and lowest in Gitelman's syndrome group. Highest level of renal K^+ loss is seen in Gitelman's syndrome followed by d RTA whereas it is normal in SPP and TPP.

HPP (SPP and TPP) required lower potassium chloride supplementation. Rebound Hyperkalemia (serum K^+ >5 mEq/L) after recovery occurred in 2 patients in SPP group and 1 patient in TPP. None of the secondary HP patients had rebound hyperkalemia.

Characteristics of patients with Gitelman's syndrome

S.No	Weight Kg	Age of onset Yrs	Sex	Tetany	Spot URINE Cl^- mmol/l	24 U Ca^{2+} mg/day	sr Ca^{2+} mg/dl	sr Mg^{2+} mg/dl
1	62	35	M	Neg	167	110	8.9	1.6
2	71	36	M	Neg	116	127.5	8.9	1.2
3	54	37	M	Pos	52	105	8.5	0.9
4	61	32	M	Pos	76	123	7.8	0.87
5	64	30	M	Neg	121	109	9.1	1.4
6	51	38	F	Neg	56	103	9	1.5

All the patients with Gitelman's syndrome had increased urinary chloride, hypocalciuria and hypomagnesemia. One patient with Gitelman's syndrome had hypocalcemia and 2 patients had tetany.

Characteristics of Sjogren's syndrome patients

S.No	Age of onset	Sex	Ocular/oral symptoms	Schirmer's	SSA & SSB	Lip Bx	Nephrocalcinosis
1	41	F	Pos	Pos		Pos	Pos
2	48	F	Pos	Pos		Pos	Neg
3	47	M	Pos	Pos		Pos	Neg
4	30	F	Neg	Pos	Pos	Pos	Neg
5	36	F	Pos	Pos	Pos	Pos	Pos
6	40	F	Pos	Pos		Pos	Neg
7	50	F	Pos	Neg		Pos	Neg

Sixteen patients had renal tubular acidosis out of which 7 had Sjogren's syndrome. Out of seven patients of Sjogren's syndrome, 1 patient had p RTA and six had d RTA. All but one patient had xerostomia and xerophthalmia.

DISCUSSION

In this study in a South Indian population there were 47 patients who fulfilled the inclusion criteria of whom 24(51%) had HPP with potassium shifts, out of which 20(43%) had sporadic periodic paralysis (SPP) and 4 (9%) had non familial Thyrotoxic periodic paralysis. Twenty three patients (49%) had non-HPP (due to potassium deficit), out of which 16 (33%) had renal tubular acidosis (15 d RTA and 1 p RTA), 6 (13%) had Gitelman's syndrome and one patient had Liddle's syndrome.

Cause of HP in various studies

	n	FPP n (%)	SPP n (%)	TPP n (%)	d RTA n (%)	p RTA n (%)	GS n (%)	PA n (%)	Liddle	Others
Lin SH et al 2001[14]	97	2(2)	29(30)	39(40)	6(6)	0	6(6)	6(6)	0	
Lin SH et al 2004[2]	43	1(2)	9(21)	20(47)	5(12)	1(2)	4(9)	1(2)	0	2(4)
Rao et al[1]	31	0	2(6)	2(6)	13(42)	0	1(3)	13(42)	0	
Maurya et al[43]	30	0	17(57)	5(17)	3(10)	1(3)	4(13)	0	0	
Phakdeekitcharoen et al[42]	34	5 (15)	10 (29)	11 (32)	8 (24)	0	0	0	0	
Our study	47	0	20(43)	4(9)	15(31)	1(2)	6(13)	0	1(2)	

In a large series of 97 patients in Taiwan in 2001, Lin SH et al reported TPP in 39 (40%), SPP in 29 (30%), Bartter's/Gitelman's in 6 (6%), d RTA in 6 (6%), and Primary Hyperaldosteronism (PH) in 6 (6%). Overall, 66 patients (68%) accounted for secondary causes.[14]

In another series reported by the same authors in 2004, out of 43 patients 9 (21%) had SPP, 20 (47%) had TPP, 6 (13%) had RTA, 4 (9%) had Gitelman's

syndrome and 1 (2%) had Primary Hyperaldosteronism. Secondary causes accounted for 33 cases (76%).[2]

Rao et al published a series of 31 cases from South India, 2 each had SPP and TPP, 13 (42%) had d RTA, 1 (3%) had Gitelman's syndrome and 13 (42%) had Primary Hyperaldosteronism.[1]

In a series by Phakdeekitcharoen et al from Thailand of the 34 patients, 11 (32%), 8 (24%) and 15 (44%) had TPP, d RTA, SPP respectively.[42]

In another study from North India, Maurya et al reported HP in 30 patients, 17 (56.7%) had primary idiopathic hypokalemic paralysis, 5 (16.7%) had TPP, 4 (13.3%) had RTA and 4 (13.3%) had Gitelman's syndrome.[43]

In most Asian studies TPP is observed as the most common cause of HP, [18,44] whereas in Caucasians, FPP is more common.[45] In our study and the study by Maurya et al, SPP is the commonest group and no FPP is reported. [43] In the study by Rao et al, HP due to Primary Hyperaldosteronism (PH) and d RTA are the most common causes.[1] None of our patients had Primary Hyperaldosteronism (PH). The difference in etiology of HP in our study and Rao et al's study may be due to difference in study setting. Our study was conducted in a tertiary nephrology practice, where as Rao et al's study was undertaken in a tertiary endocrinology practice.

Data of HPP in various studies

	FPP n (%)	SPP n (%)	Mean age at onset yrs	M:F
Lin SH et al 2001[14]	2(2)	29(30)	21	25:6
Lin SH et al 2004[2]	1(2)	9(21)	27	9:1
Rao et al[1]	0	2(6)	13	2:0
Maurya et al[43]	0	17(57)	32	17:0
Phakdeekitcharoen et al[42]	5(15)	10(29)	22	13:2
Our study	0	20(43)	25	15:5

In our study 20 patients (43%) had SPP, none had family history of periodic paralysis. The mean age of onset was 24.6±5.7 yrs with a male preponderance 15:5. The mean duration of weakness was 22.7±5 hrs. The mean potassium chloride (both oral and intravenous) required for recovery of paralysis in this group is 58±23 mmols (range 20-110 mmols). None had urinary loss of potassium in this group.

Three patients had respiratory paralysis in this group. Thirteen patients noticed weakness while getting up from bed in the morning, 1 patient noticed weakness after recovering from alcohol binge. Limb muscles were more affected than the trunk muscles. Those who had respiratory paralysis and muscle power ≤3/5 where treated with intravenous potassium chloride and others were treated with oral potassium supplementation. All patients were started on acetazolamide or spiranolactone prophylaxis. Four patients in this group had recurrence between 4-10 weeks after discontinuation of prophylaxis.

Data of TPP in various studies

	n (%)	Mean Age Yrs	M/F	T3(nmol/L)	T4 (nmol/L)
Lin SH et al 2001[14]	39(40)	28	39:0	4.5±0.2	201±33
Lin SH et al 2004[2]	20(47)	28	20:0		
Rao et al[1]	2(6)	36	2:0		
Maurya et al[43]	5(17)	36	5:0		
Phakdeekitcharoen et al[42]	11(32)	32	10:1		
Philip Wong et al[46]	10	34	9:1		
Our study	4(9)	43	3:1	5.7±0.1	196.25±5

We had 4 patients (9%) with TPP with a mean age of 43 yrs, M: F, 3:1. The incidence of TPP is highest in Asian population which accounted 80% in Hong Kong[18] and 40% in Taiwan.[14] But TPP is not the most common causes in our study and other Indian studies. [43,1] All the four patients in our study had tachycardia without any overt thyrotoxic symptoms. These findings in our study are in conformity with other studies which states that TPP affects males more than females although thyrotoxicosis is common in females and most patients have only mild or no symptoms of thyrotoxicosis . [46, 47] These patients were managed with oral potassium and propranolol followed by definitive therapy for thyrotoxicosis. We did not see recurrences in this group of patients.

Data of RTA patients in various studies

	No of patients		Mean Age Yrs	M:F	Sjogrens	Nephro calcinosis
	p RTA	d RTA				
LIN SH et al 2001[14]	0	6	47	3:3	3	
LIN SH et al 2004[2]	1	5	39	3:3	4	
Rao et al[1]	10	3	33	9:4	3	
Maurya et al[43]	1	3	27	1:3		
Phakdeekitcharoen et al[42]	0	8	41	1:3		3
Our study	1	15	37	4:12	7	2

The cause of HP in 16 patients (33%) in our series was Renal tubular acidosis (15- distal RTA and 1- proximal RTA), 7 patients had Sjogren's syndrome. All the patients had high renal potassium excretion (U K^+/Cr 4.35±0.8). As shown above the patients with RTA were predominantly females with mean age of 37 yrs. Mean time to improve was higher (31.3±6.2 Vs 22.7±5.07 hrs) than SPP, and required more potassium supplementation (101.3±18.8 Vs 58±23 mmols) for paralysis recovery than in SPP. Two patients had respiratory paralysis which improved after potassium supplementation. Pun et al described 26 patients with Sjogren's syndrome, 3 had HP and distal RTA which preceded diagnosis of Sjogren's syndrome by 2-8 years. [49]

Data of GS patients in various studies

	n (%)	Mean Age	M:F
Lin SH et al 2001[14]	6(6)	21	4:2
Lin SH et al 2004[2]	4(9)	24	3:1
Rao et al[1]	1(3)	68	1:0
Maurya et al[43]	4(13)	29	4:0
Phakdeekitcharoen et al[42]	0		
Our study	6(13)	35	5:1

In our series 6 (13%) had Gitelman's syndrome, mean age 34.67±3.1yrs, with 5 males and 1 female. These patients had low serum chloride (97.83±5.8 Vs 105±13.5 mEq/l) than SPP. Two of our patients had history of tetany with low serum calcium (7.8 and 8.5 mg/dl). None had respiratory paralysis.

In Lin SH et al (2001)[14] series they reported 6 cases of Bartter's/Gitelman's, individual case reports of Bartter's syndrome with HP were reported[50.] None of our patients had Bartter's syndrome.

GS patients were treated with magnesium and potassium supplementation. Potassium sparing diuretics and indomethacin can also be used.[41, 51] It is essential to correct hypomagnesemia along with hypokalemia, otherwise hypokalemia will be resistant to correct if there is underlying magnesium deficiency. [41]

In our study one male patient who presented with HP had Liddle's syndrome, he was diagnosed to have hypertension about one year before presentation. He had recurrent episodes of HP in the year 2009. BP remained

high despite being on 4 antihypertensives (telmesartan, thiazide, prazosin, metaprolol). He had metabolic alkalosis with urinary potassium loss, low plasma renin activity and low aldosterone. He had good response to triamterene and did not have recurrence. There are case reports of muscle weakness[52] and periodic paralysis[53] in Liddle's syndrome.

In our study three patients had rebound hyperkalemia (>5 mEq/L), two patients in SPP and one patient in TPP groups. None of the patients in Non- HPP (large K^+ deficit) group had rebound hyperkalemia. In Lin SH et al (2004)[2] series 19 of 30 patients in the HPP group developed rebound hyperkalemia.

Since this study is from a single tertiary referral centre, only those patients with severe or recurrent episodes may have been seen by us. This is a limitation of our study.

CONCLUSIONS

1. The commonest causes for hypokalemic paralysis (HP) in our study were sporadic periodic paralysis (SPP) and renal tubular acidosis (RTA).

2. Among the patients with hypokalemic paralysis, 57% of them were due to secondary causes. Presence of acidosis or alkalosis in arterial blood gas analysis suggests a renal cause for Hypokalemic paralysis.

3. Spot urine K^+/Cr ratio helps to distinguish the diagnostic categories of HPP (Hypokalemic paralysis due to K^+ shifts) with non-HPP (Hypokalemic paralysis due to K^+ deficits)

4. There was a male predominance in Hypokalemic periodic paralysis (HPP). Sporadic periodic paralysis (SPP) was more common than familial periodic paralysis (FPP) in this study.

5. Male predominance was noted in Thyrotoxic periodic paralysis (TPP). Absence of history of thyroid disease or clinical thyrotoxicosis does not exclude the diagnosis of TPP. So thyroid function tests should be done in all patients with HP.

6. Though much less potassium is needed during therapy of HPP (SPP, TPP), there is still a danger of rebound hyperkalemia.

7. Hypomagnesemia should be looked for and corrected along with the correction of hypokalemia in patients with metabolic alkalosis.

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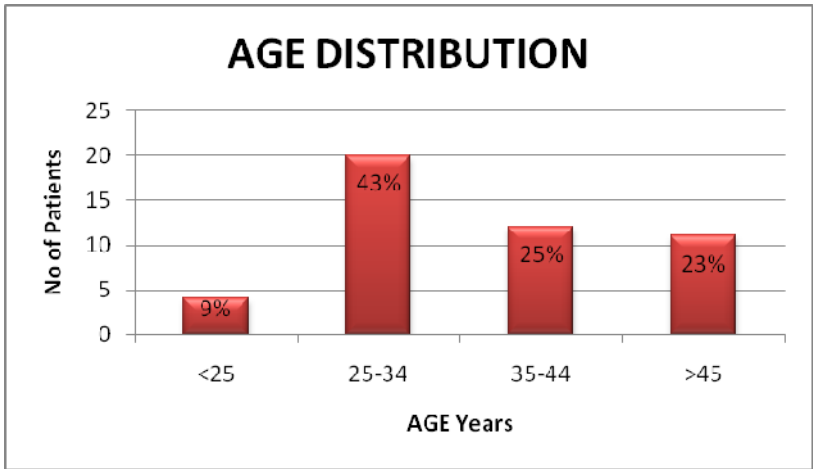
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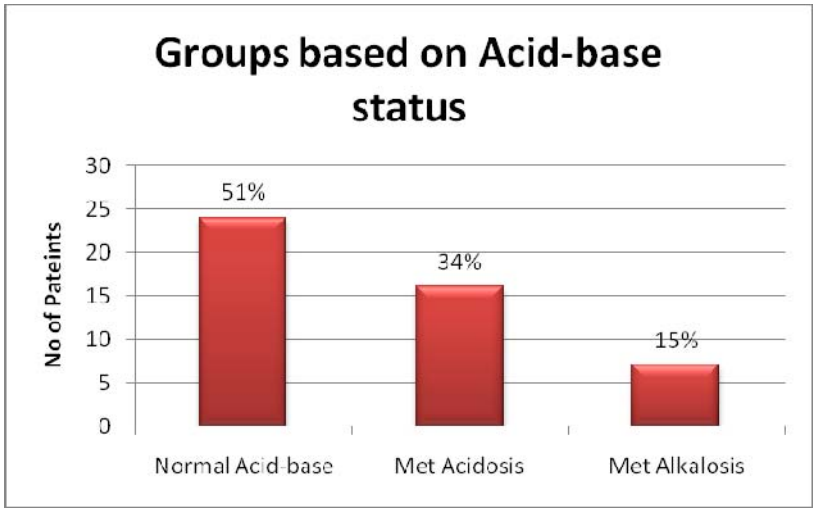
AGE Years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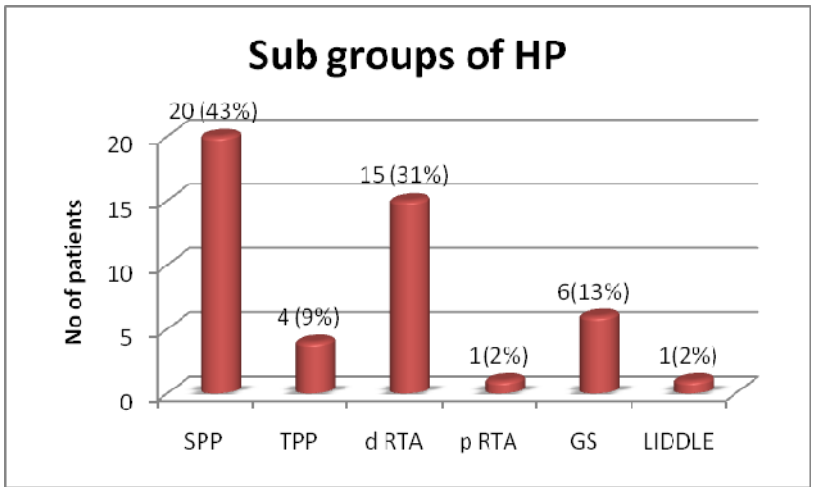
Met Alkalosis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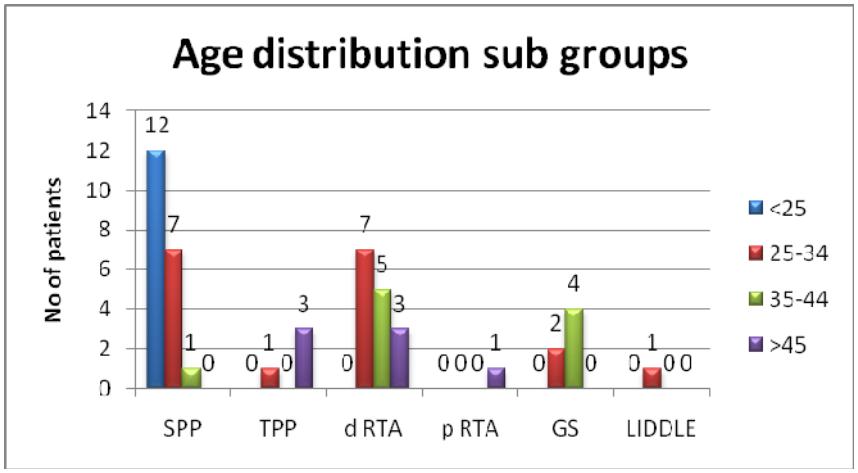
SPP
TPP
d RTA
p RTA
GS
LIDDLE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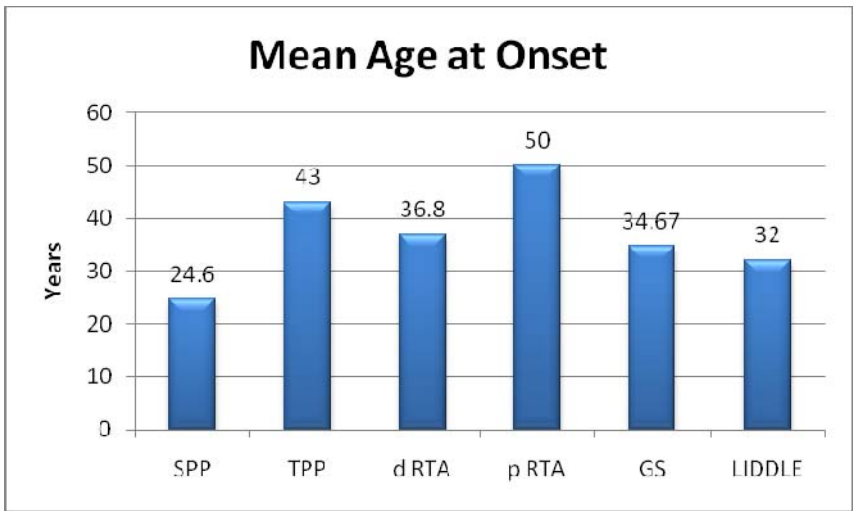
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p RTA
GS
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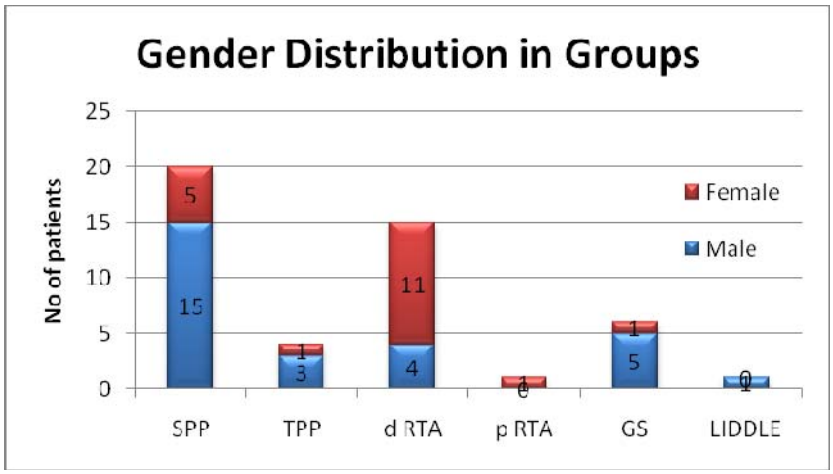
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GS
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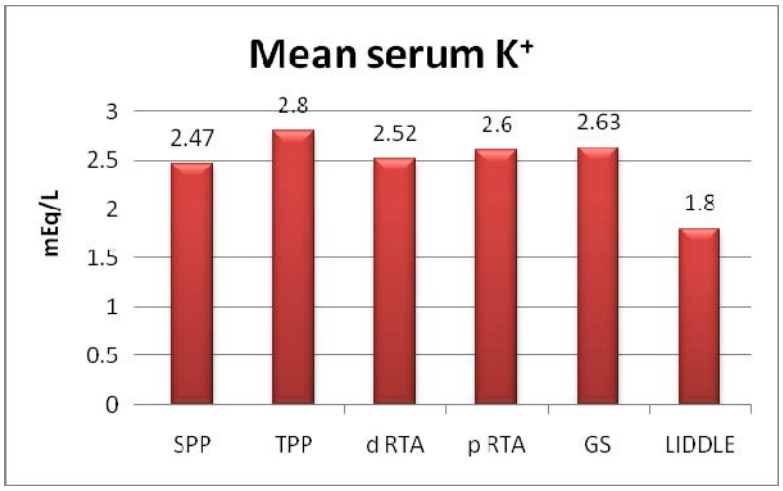
Male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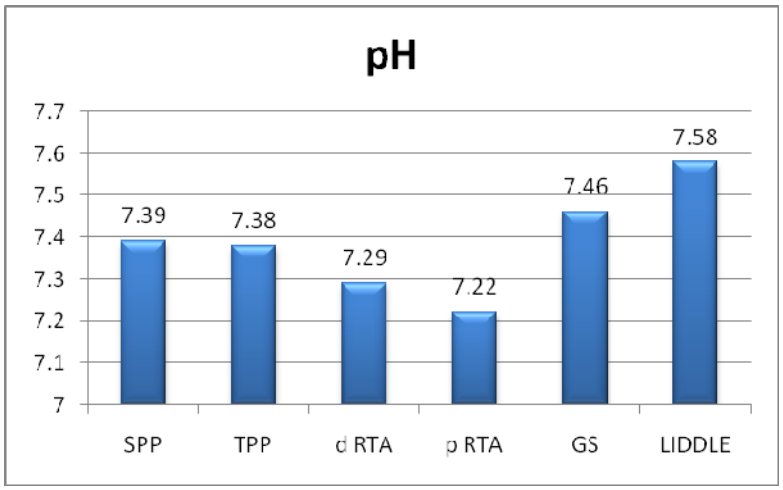
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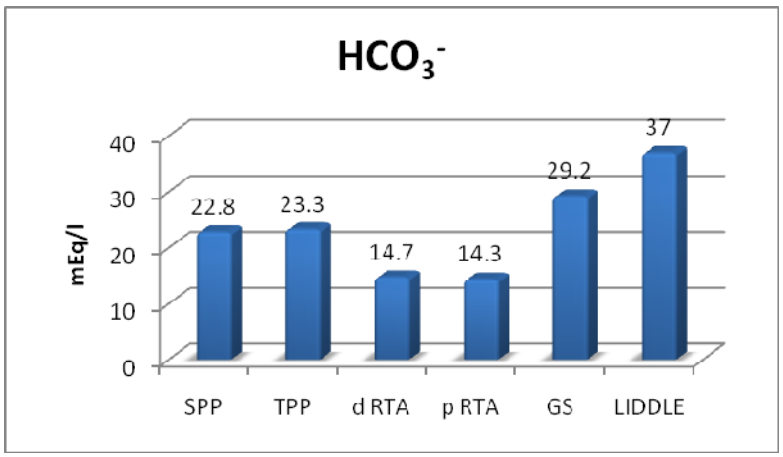
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TPP
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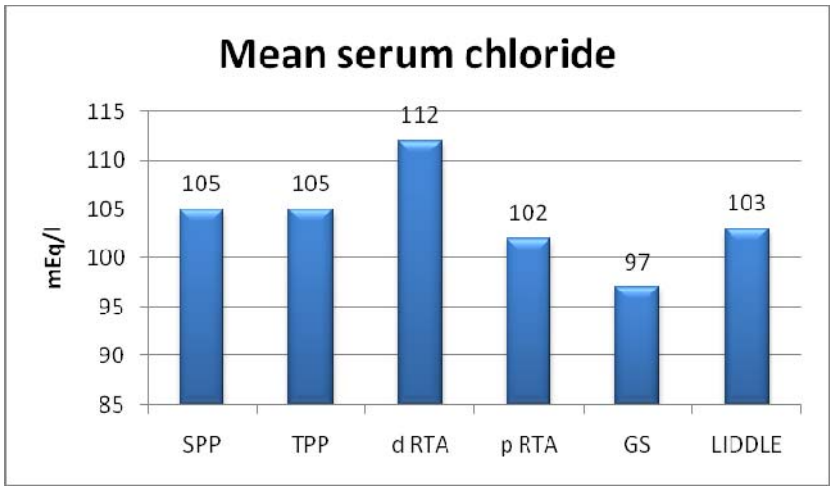
GS
LIDDLE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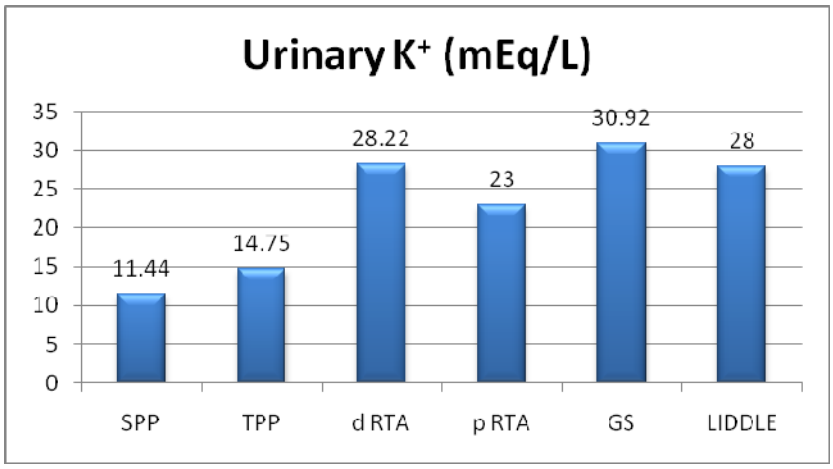
TPP
d RTA
p RTA
GS
LIDDLE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5
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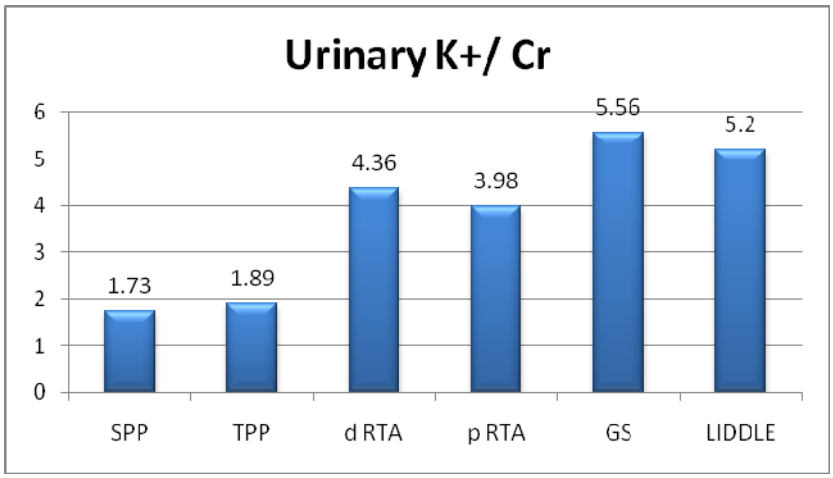
14.75
28.22
23
30.92
28
SPP
TPP
d RTA
p RTA
GS
LIDDLE


Urinary K+/ Cr
6
5
4
3
2
1
0
1.73
1.89
4.36
3.98
5.56
5.2
SPP
TPP
d RTA
p RTA
GS
LIDDLE

MASTER CHART

S.NO	Age of onset (yr)	weight (kg)	Sex	No Of episodes	Time to improve (hr)	Kcl required till recovery (mmol	Duration of Illness (mo)	Resp Paralysis	sr K+ (mmol/L)	sr Na+ (mmol/L)	B sugar (mg/dl)	B.Urea (mg/dl)	sr Cr (mg/dl)	Sr Po4 (mg/dl)	sr Ca (mg/dl)	sr Mg (mg/dl)	pH	pCO2	HCO3 (mmol/L)	Cl(mmol/L)	U K+(mmol/L)	U Cr(mmol/L)	U K+/U Cr	U Cl(mmol/L)	24 U Ca(mg/dl)	U.pH	T3 (nmol/L)	T4(nmol/L)	SHIRMERS	U. ACIDIFI	pulse	BP	Aminaciduria	FE PO4	DIAGNOSIS	RECURRENCE	Rebound Hyper K+
1	32	45	F	3	26	150	24	N	2.5	139	102	20	1	3.3	8.7	2	7.26	36.3	15.6	102	39	7.2	5.42	81		5.9	78	4.2	NEG	>5.5	78	120/70	NIL	8.9	d RTA		N
2	42	52	M	6	36	90	42	N	2.3	140	74	23	1	2.6	9.2	2.1	7.23	29.9	15	120	29	7.8	3.72			6.5	96	3.5	NEG		82	110/70	NIL	12.6	d RTA		N
3	29	53	F	3	24	100	14	N	2.8	141	95	28	0.7	4.2	9	1.9	7.34	33.9	18.9	118	31	6.8	4.56			5.9	79	6.2	NEG	>5.5	76	120/80	NIL	14	d RTA		N
4	28	56	M	6	25	120	24	N	3.8	133	92	22.8	0.6	3.5	9.2	1.9	7.36	25	13.8	108	16	4.8	3.33		198	5.9	102	5.6	NEG		95	120/80	NIL	9.8	d RTA		N
5	33	49	F	2	35	190	1	Y	1.8	136	109	18	0.6	3.8	9.5	2.1	7.37	21.1	12	112	30	5.8	5.17			5.8	85	4.3	NEG	>5.5	82	116/70	NIL	14	d RTA		N
6	26	58	M	7	36	100	28	N	2.8	134	90	18	0.6	2.9	8.9	2.3	7.36	24	13.5	110	17	3.9	4.36		198	6	102	5.6	NEG		96	120/80	NIL	7.8	d RTA		N
7	32	46	F	3	38	90	4	N	1.9	135	99	21	8	2.7	9	1.9	7.37	21.8	12.4	108	29	7.8	3.72			5.9	86	4.1	NEG	>5.5	89	116/70	NIL	14	d RTA		N
8	42	62	F	2	26	190	12	Y	1.7	140	95	26	8	4.1	8.9	2.1	7.25	39.3	17	123	26	6	4.33			5.7	75	4	NEG		78	110/70	NIL	12	d RTA		N
9	46	61	F	2	39	120	20	N	2.3	142	95	26	1	3.9	8.9	2	7.26	37.6	15.9	114	25	5.9	4.24			5.7	75	4	NEG		108	110/70	NIL	9.8	d RTA		N
10	38	56	M	7	19	110	36	N	2.1	139	90	27	0.9	4.3	9		7.39	41.4	24	109	11	7.3	1.51			5.8	78	5.2			78	120/80			SPP	Y	N
11	24	62	F	1	19	50		N	2.7	136	102	25	0.7	3.6	9.2		7.38	42	22	108	14	7.9	1.77			5.7	82	5.6			96	110/70			SPP		N
12	34	60	M	2	23	50	11	N	1.9	138	85	31	1.1	4.1	8.9		7.36	37	22	102	9.5	5.72	1.66			5.9	76	4.5			98	120/82			SPP		5.6
13	22	48	F	7	32	60	24	N	1.9	136	92	26	0.8	3.1	8.8		7.37	41	22.2	105	11.5	6.2	1.85			6.5	95	5.3			89	124/84			SPP		N
14	30	54	M	2	30	20	5	N	2.2	131	88	18	0.8	3.2	9		7.39	40.6	23.2	101	10	5.8	1.72			5.9	82	7.2			79	130/80			SPP		N
15	28	52	M	7	25	90	11	N	2.6	136	99	24	0.7	3.4	9.2		7.4	44	23.1	99	6.3	5.71	1.10			5.9	96	5.2			88	13/80			SPP	Y	N
16	18	61	M	1	26	80		N	1.8	138	102	26	0.7	3.6	8.9		7.38	42	20	106	7	6.2	1.13			5.6	89	3.9			96	120/80			SPP	Y	N
17	20	53	M	3	19	170	23	Y	1.8	137	85	20	0.8	3.5	9.5		7.38	42	22.2	99	12	8.4	1.43			5.6	78	4		<5.5	95	120/80	NIL		SPP		N
18	21	51	M	2	22	60	3	N	3	134	98	18	0.7	3.6	8.9		7.4	36	22	100	11	5.6	1.96		212	6.2	112	5.8			82	130/80			SPP		N
19	22	43	F	1	24	40		N	2.6	134	79	18	0.55	3.4	8.5		7.36	36	23	106	12	6.7	1.79			5.7	78	5.2			99	110/70			SPP		N
20	20	62	M	2	34	90	3	N	3.1	133	90	22	0.7	3.5	8.8		7.39	41	23	105	11	6.2	1.77			5.6	96	4.5			87	110/80			SPP	Y	N
21	19	49	M	6	22	160	24	Y	1.9	138	92	26	0.9	2.8	9.1		7.39	41.2	23.9	107	12	6.3	1.90			5.7	98	5.2			78	120/80			SPP		N
22	19	45	M	2	20	50	2	N	2	135	99	24	0.7	2.9	9.2		7.38	42	22.3	109	13	8.2	1.59			5.8	89	5.6			96	110/70			SPP		5.1

23	23	52	M	3	28	160	7	Y	2	136	85	25	8	4	8.5		7.36	36.9	22	101	9.5	5.78	1.64			5.9	79	7			79	120/80			SPP		N
24	32	48	F	2	18	60	2	N	2.9	134	89	20	0.6	2.8	8.8		7.35	35.8	22.9	108	12	8.2	1.46			5.7	88	5.6			102	110/70			SPP		N
25	30	54	M	2	20	70	3	N	3.2	133	88	24	0.7	3.6	8.5		7.39	41	23	105	11	8.2	1.34			5.6	96	4.5			85	110/80			SPP		N
26	25	52	M	2	21	30	3	N	1.9	140	98	23	0.9	2.8	9		7.38	42.6	22.6	109	12	6.5	1.85			6.1	95	3.8			102	120/80			SPP		N
27	26	49	F	2	18	30	5	N	3	141	96	18	0.6	3.5	9.3		7.38	41.4	24.4	108	16	6.6	2.42		214	5.6	82	4			86	120/80			SPP		N
28	19	56	M	2	15	40	1	N	2.9	135	102	22	0.9	3.6	8.5		7.41	43	24.1	102	14	6.2	2.26		245	5.7	99	5.9			75	130/80			SPP		N
29	22	50	M	2	19	60	5	N	2.9	140	102	21	0.8	3.4	8.6	2.1	7.40	37.1	24.1	111	14	5.8	2.41			5.6	87	5.6			75	130/80			SPP		N
30	35	62	M	1	32	120		N	2.5	135	96	25	0.8	4.1	8.9	1.6	7.46	37	26.5	105	25.6	4.8	5.33	167	110	5.6	79	3.9			84	130/80			GS		N
31	36	71	M	2	38	100	14	N	3.1	136	95	26	0.8	2.9	8.9	1.2	7.5	44.5	34	89	31	5.8	5.34	116	127.5	5.9	89	5.4			78	120/80			GS	Y	N
32	37	54	M	2	47	80	14	N	2.8	135	109	19	0.7	3.8	8.5	0.9	7.45	41.5	27.8	103	28	3.9	7.18	52	105	5.8	102	5.6			82	130/80			GS		N
33	32	61	M	1	30	90		N	3	126	92	24	1	3.7	7.8	0.87	7.42	46.1	29	98	36	7.8	4.62	76	123	6	96	7.5			89	130/80			GS		N
34	30	64	M	1	36	80		N	1.9	136	99	25	0.9	3.3	9.1	1.4	7.48	42.3	28.5	98	42	6	7.00	121	109	5.9	85	6			98	120/80			GS		N
35	38	51	F	2	42	70	16	N	2.5	135	88	26	0.9	2.8	9	1.5	7.47	42.1	29.8	94	22.9	5.9	3.88	56	103	5.9	103	4.2			82	130/80			GS		N
36	41	50	F	3	23	90	14	N	2.1	140	113	23	0.8	4	8.8	2	7.24	26.6	11.3	123	40.3	7.3	5.52			6.6	84	5.4	POS	>5.5	96	120/80	NIL	12	d RTA/SJ		N
37	48	52	F	1	32	90		N	3	136	73	24	0.7	4.2	8.5	1.9	7.33	27	14	112	32	7.9	4.05			5.6	78	5.4	POS	>5.5	95	120/70	NIL	14	d RTA/SJ		N
38	47	49	M	2	30	100	1	N	2	140	109	18	0.6	3.8	8.6	1.8	7.33	27.9	15	115	26	5.72	4.55			5.9	82	6.1	POS	>5.5	82	110/70	NIL	9.1	d RTA/SJ		N
39	30	45	F	4	41	110	6	N	2.5	138	99	20	0.7	3.2	8.9	2	7.24	36.7	15.6	110	32	6.2	5.16			5.6	89	4.5	POS		99	120/70	NIL	7.8	d RTA/SJ		N
40	36	46	F	2	24	80	2	N	2.9	139	80	22	0.7	3	8.8	2.1	7.26	39.2	16.8	102	29	6.3	4.60			5.6	98	5.6	POS		87	110/70	NIL	11	d RTA/Sj		N
41	40	60	F	3	35	90	24	N	2	139	95	24	0.9	4.1	8.5	2.3	7.23	30.1	15.1	103	22	8.2	2.68			5.9	82	5.6	POS	>5.5	79	110/70	NIL	15.2	d RTA/SJ		N
42	50	58	F	3	24	80	4	N	2.6	138	102	24	0.7	3.2	8.6	2	7.22	35.6	14.3	107	23	5.78	3.98			5.7	75	3.2	POS	<5.5	89	110/70	NIL	26	p RTA/SJ		N
43	49	54	M	2	28	70	10	N	2.3	140	102	26	0.7	3.4	8.6		7.36	39.3	23.6	110	16	8.8	1.82			5.8	202	11.8			102	120/80			TPP		N
44	30	52	M	2	21	80	3	N	2.9	138	102	24	0.7	3	9.2		7.38	41.8	21.8	108	15	6.2	2.42			5.7	198	8.9			112	120/80			TPP		N
45	45	61	F	1	27	40		N	2.9	138	90	24	1	2.9	9		7.38	42	24.1	104	12	6.5	1.85			5.9	226.5	16			110	130/80			TPP		5.2
46	48	53	M	1	19	40		N	3.1	132	79	25	0.9	2.8	9.5		7.38	41.2	23.6	98	16	7.1	2.25			5.6	195	12.1			108	120/80			TPP		N
47	32	54	M	3	12	50	3	N	1.8	144	78	26	1	3	9	2.3	7.58	35	37	103	28	5.3	5.28		201	6.5	78	4			78	160/100			LIDDLE		N

PROFORMA

1. Name: NC No.: DOA:

2. Age: Sex:

3. Occupation:
4. Address:

5. Presenting History:

    a. Vomiting:
    b. Diarrhoea:
    c. Drugs:
    d. Laxative abuse:
    e. Other predisposing Factors:
    f. Fever:
    g. Polyuria:
    h. Dry eyes:
    i. Dry mouth:
6. Family History:

7. Examination:

		Rt	Lt
Power	UL		
	LL		
DTR	UL		
	LL		
Neck muscles			
Resp Paralysis			

8. Vital signs:

    Pulse: BP: RR:

a. Systems:

9. Previous episodes:

10. Treatment:

11. Investigations :

Sl No.	Test				
1	ECG				
2	TC				
3	DC				
4	ESR				
5	Hb				
6	UREA				
7	CREATININE				
8	B.SUGAR				
9	Sr Na				
10	Sr K				
11	Sr Po4				
12	Sr calcium				
13	Sr uric acid				
14	Sr osmolality				
15	ABG				
16	URINALYSIS				
		Protein			
		Sugar			
		Deposits			
17	URINE CULTURE				

18	URINE pH			
19	URINE K			
20	URINE Cl			
21	URINE PO4			
22	URINE UA			
23	Urine amino acids			
24	Urine osmolality			
25	TTKG			
26	24 urine Ca			
27	Ca/Cr Ratio			
28	Sr Mg			
29	NCS			
30	Thyroid profile			
31	U Acidification test			
	ABG			
	Urine pH			
32	KUB			
33	USG			
34	CT KUB			
35				
36				
37				
38				
39				
40				

Diagnosis

Follow up