

Chronic Persistent Hypokalaemia in Children

K Akl, J Albaramki

ABSTRACT

Objective: Chronic hypokalaemia is a cause of morbidity and mortality. The purpose of this study is to determine the aetiology of chronic hypokalaemia in children at a tertiary care hospital setting.

Methods: Retrospective medical record review of consecutive cases of persistent chronic hypokalaemia of more than three months duration.

Results: There were 51 patients with chronic hypokalaemia. Females were 55%. Mean age was 8 years (range 1 month to 18 years). Metabolic alkalosis, metabolic acidosis were found in 30/51(58.8%), and 19/51(37.2%) respectively. Normal blood pressure was found in 23/30 (76.7%) of patients with metabolic alkalosis. Bartter syndrome was diagnosed in 21 patients. Hypertension was found in 6/30 (20%) patients with metabolic alkalosis. Four had apparent mineralocorticoid excess. Distal renal tubular acidosis (dRTA) was the most common cause in the metabolic acidosis group followed by Fanconi syndrome.

Conclusion: In cases of hypokalaemia, patients may be divided according to the acid base balance. Those with metabolic alkalosis may be divided into those with normal blood pressure and those with hypertension. Focused history, physical examination, especially volume status and spot urinary chloride helps in the differential diagnosis of normotensive cases with metabolic alkalosis.

Keywords: Children, chronic, hypokalemiaetiology, Jordan

From: Department of Paediatrics, Jordan Univeristy Hospital, The University of Jordan Amman, Jordan.

Correspondence: Dr K Akl, Department of Paediatrics, Section of Pediatric Nephrology, The University of Jordan, POB 13046- Amman, Jordan. Fax: 00962 6 5353388, e-mail: kamp.akl28@gmail.com

INTRODUCTION

Potassium is the most abundant cation in the body, with 98% being intracellular and 2% extracellular. The resting membrane potential needs a high intracellular potassium concentration to be maintained. The generation of the action potential is governed by the status of the resting potential. The action potential and cell excitability is altered by any change in the serum potassium concentration, thus resulting in clinical manifestations of hypokalemia. While acute hypokalaemia is common in practice, persistent chronic hypokalaemia is not. Almost all the reports in the literature tackle acute hypokalaemia (1-3).

The only reports on chronic hypokalaemia are those dealing with renal tubular disorders, which do not give a true reflection since normokalaemic patients were mixed with hypokalaemic ones (4). Causes of hypokalemia include hormonal, hormonal, drugs, cellular uptake of potassium, renal and gastrointestinal losses .The most common renal tubular disorders as reported by Kiran et al were dRTA(44%), followed by BS(22%), and Fanconi syndrome(13%)(4).

The aim of this study is to find out the most frequent causes and develop a practical approach to the diagnosis of chronic persistent hypokalaemia in children at a tertiary care hospital.

METHODS

The medical records of children with chronic persistent hypokalaemia admitted to the Jordan University Hospital over a ten year period from June 2005 to June 2015 were reviewed for aetiology, age at onset, sex, presentations, and complications. Included: All consecutive cases of persistent decrease in serum potassium below 3.5 mmol/L, of > 3 months duration. Excluded:

Intermittent and transient hypokalaemia of less than 3 months duration. Hypokalaemia was defined as mild, moderate, and severe if the serum potassium was 3.0-3.5 mmol/L, 2.5- 3.0 mmol/L, and <2.5 mmol/L respectively.

Hypokalaemia was empirically defined as chronic if it persisted for more than 3 months. Metabolic acidosis was defined as pH < 7.35 with reduced plasma bicarbonate(<24 mmol/L) and metabolic alkalosis defined as pH > 7.45 with elevated plasma bicarbonate of more than 28-30 mmol/L. Nephrocalcinosis was defined as renal parenchymal calcification on ultrasonography. The study was approved by the University of Jordan/ Faculty of Medicine Ethics Committee.

RESULTS

Average annual hospital admissions to the paediatric ward were 3014 patients. Chronic persistent hypokalaemia occurred in 5.2 children per year. There were 51 cases. Males were 23/51(45%), females 28/51(55%). Age ranged from 1 month to 18 years. Mean age at diagnosis was 8 months (range: 1 month to 15 years). Follow-up ranged from 3 months to 14 years. Ten patients needed admission to the intensive care unit for cardiac monitoring during intravenous potassium administration.

Table: Causes of Chronic hypokalaemia in children

Diagnosis	Number (%)	Age of onset: medium (Range)
Metabolic Alkalosis with normal/low blood pressure		
<i>Bartter syndrome</i>	21(41.18%)	2 mo(1mo-8 y)
Metabolic Alkalosis with elevated blood pressure		
<i>AME</i>	4(8%)	8 mo(6 mo-9 y)
<i>CAH</i>	1(2%)	1 mo
Metabolic Acidosis		
<i>dRTA</i>	13(25.5%)	8 mo(2mo-15y)
<i>Fanconi syndrome</i>	6(11.76%)	9 mo(6mo-2y)
<i>Unknown</i>	6(11.76%)	-

dRTA: distal renal tubular acidosis; AME: apparent mineralocorticoid excess; CAH: congenital adrenal hyperplasia.

Metabolic alkalosis with normal blood pressure

Bartter syndrome (BS)

Polyhydramnios occurred in 6/21(29%), presence of parental consanguinity in 11/21(52%), and similar cases in the family in 7/21(33%). Failure to thrive (FTT) occurred in 15/21(71%), vomiting in 12/21(57%), recurrent dehydration in 14/21(67%), muscle weakness/paralysis in 6/21(29%), constipation in 5/21(24%), and polyuria in 9/21(43%). The vomiting which was severe and recurrent in 4, resolved with potassium repletion. All patients were normotensive, had hypokalaemic metabolic alkalosis and elevated urinary potassium and chloride. Hyperuricemia was found in 6/9 tested (67%) nephrocalcinosis in 10/21(48%), renal cysts in 1/21(5%), and end stage renal failure (ESRF) in 5/21(24%). Chronic diarrhoea occurred in 1 patient. Renal biopsy was done for one patient with chronic kidney disease (CKD), hyperuricemia and nephrocalcinosis. It showed glomerular global sclerosis with interstitial fibrosis. Patient reached end stage renal failure (ESRF). Severe hypokalaemia occurred in 7/17, and mild hypokalaemia in

2/17 patients. The lowest serum potassium was 1.6 mmol/L. One infant developed a transient bulging fontanelle, which resolved after treatment of hypokalaemia. Two children with Bartter syndrome were initially diagnosed as nephrogenic diabetes insipidus because of the polyuria. Death occurred in 4/21(19%) from renal failure.

Metabolic alkalosis with elevated blood pressure

Apparent Mineralocorticoid Excess (AME)

Family history was positive in 3/4(75%). FTT occurred in 3/4, muscle weakness in 4/4. Headache in 2/4, forgetfulness in 1/4 patients, and irritability in 2/4 patients, paralysis in one. All AME cases who were confirmed by genetic testing, had hypokalaemic metabolic alkalosis with severe hypertension. One case developed infarction pattern on EEG from the severe hypokalemia (serum K 1.7 mmol/L) *Congenital Adrenal Hyperplasia(CAH)* : One patient with *11B* hydroxylase deficiency had recurrent muscle weakness with paralysis, paresthesias, muscle cramps, hypertension, vomiting, and a bone cyst.

Metabolic acidosis

Distal Renal Tubular Acidosis Type I (dRTA I)

Parental consanguinity occurred in 6/13(69%), similar cases in 6/13(77%), failure to thrive occurred in 7/13(54%), vomiting in 5/13(38%), dehydration in 2/13(15%), hearing deficit in 4/13(31%), polyuria in 5/13(38%), muscle weakness in 6/13(46%), paralysis in 4/13(31%) constipation in 3/13(23%), and spherocytosis in 1/13(8%). All had normal anion gap hyperchloremic metabolic acidosis with a positive urine anion gap. Nephrocalcinosis occurred in 10/13(77%), and renal cysts in 3/13(23%). Sensorineural hearing loss occurred in 3/13 patients. One female was initially diagnosed as polymyositis. Classic dRTA(Type I) was found in 9/13(69.2%), and 4/13(31%) had associated low serum phosphate and uric acid. In one

patient with familial dRTA the hypophosphatemia and low serum uric acid corrected after restoration of serum potassium to normal. Ameliogenesis imperfecta was found in one patient with dRTA, and hereditary spherocytosis in another. The lowest serum potassium was 1.4mmol/L. Severe hypokalemia occurred in 6/10 patients and mild hypokalemia in 2/10 patients. Muscle paralysis was more frequent in the atypical form of dRTA.

Fanconi syndrome

Patients presented with FTT 4/4(100%), muscle weakness in 2/4(50%), polyuria 2/4(50%), and spherocytosis in 1/4(25%) patients. All patients had recurrent dehydration secondary to salt losses associated with glucosuria, hypercalciuria kaliuria, and low serum phosphate and uric acid. Two patients had glycogen storage disease Type XI, one had cystinosis, with *CTNS* gene mutation and 3 were idiopathic. One patient had associated myasthenia gravis.

Unknown: Four out of six patients had metabolic alkalosis out of whom 2 had hypertension. No genetic testing was done. Both patients had unilateral renal atrophy in the absence of a history of urinary tract infections.

DISCUSSION

In our hospital chronic persistent hypokalaemia occurred in 5.2 admitted children per year. The most common causes of chronic persistent hypokalaemia in our study were BS (41.18%), dRTA (25.5%), fanconi syndrome (11.76%), and AME (7.84%).

The first step in the evaluation of the hypokalaemic patient is to check the urinary potassium. If it is less than 20 mmol/L then most likely it is secondary to extrarenal causes. If it is >20 mmol/L then renal losses are more likely, and evaluation of acid- base status is needed.

Dividing patients into those with metabolic alkalosis, metabolic acidosis, and normal acid base balance helps in reaching a diagnosis. In case of metabolic alkalosis checking urinary chloride further separates those with saline responsive metabolic alkalosis secondary to extrarenal causes (Urine chloride < 10 mmol/L) from those with saline resistant metabolic alkalosis. Checking the blood pressure, further differentiates those with normotension from those with hypertension. In those patients with metabolic alkalosis and a normal blood pressure, Bartter syndrome accounted for the majority of our cases. AME accounted for the majority of hypertensive hypokalaemic metabolic alkalosis cases. Vomiting, which occurred in 30% of BS cases, resolved with the normalization of serum potassium. Hypokalaemia may have caused transient esophageal smooth muscle paralysis, or even gastroparesis.

While chronic hypokalaemia rarely causes renal failure, ESRF occurred in 25% of BS cases. Hypokalaemic nephropathy leads to glomerular sclerosis, interstitial fibrosis, and cyst formation as in our patient who was biopsied. Such findings were mentioned in the literature (5). The use of Ibuprofen as part of his treatment may have added further injury. The occurrence of hyperuricemia, and nephrocalcinosis which occurred in 66.6% and 48% of cases respectively remains to be determined. Hyperuricemia and even gout were described in association with BS (7). There is no definite answer on the effect of nephrocalcinosis on renal function (6). In our patients nephrocalcinosis occurred in 48% of patients with BS versus 77% in dRTA. Yet ESRF occurred in 25% of patients with BS and in none of our dRTA patients.

Severe hypokalaemia in BS is known to cause skeletal muscle paralysis (8). In our patients the muscle paralysis was more pronounced in the hypokalaemic hypertensive metabolic alkalosis group which included AME and CAH. In the metabolic acidosis group, the most common cause of muscle paralysis was the atypical form of dRTA I. In a study by Sung et al ,

the most common cause of hypokalaemic nonperiodic paralysis, was dRTA which was a main cause in adults with metabolic acidosis, while primary aldosteronism and Gitelman syndrome were the major causes in patients with metabolic alkalosis(9). Chronic diarrhoea , which was the presenting feature of BS in one of our patients, has been described in the literature(10) As in two of our patients, nephrogenic diabetes insipidus(NDI) may be the presentation of BS(11).

The most common aetiologies in the metabolic acidosis group in our study were dRTA followed by Fanconi syndrome. The rare association of dRTA type I with hereditary spherocytosis (HS) in one of our patients with dRTA and one of those with the fanconi syndrome has been described in the literature. Rarely, mutations in the gene AE1 (Anion exchanger 1; Band 3) which is shared by dRTA and HS, causes both dRTA and HS(12).

Amelogenesis Imperfecta, which manifests with enamel hypoplasia and discoloration of the teeth, may be associated with dRTA and nephrocalcinosis as found in one of our patient (13). Atypical presentation of dRTA occurred in 31% of our patients. There are few reports in the literature on atypical dRTA, which mainly occurs in people of Arabic descent (14). Tassic et al described two males siblings with dRTA associated with proximal tubular dysfunction similar to our 4 patients. The proximal tubular defects normalized after treatment with potassium and sodium bicarbonate similar to our patients (15). The unknowns accounted for 12% of the cases. Limitations of our study includes being retrospective, having a small number of patients, and paucity of genetic testing.

CONCLUSION

Chronic hypokalaemia associated with non-anion gap metabolic acidosis is usually secondary to renal tubular acidosis. If the patient has metabolic alkalosis, measuring the blood pressure differentiates those with normotension from others with hypertension. Normotensive patients, in the presence of elevated urine potassium and chloride mostly have Bartter or Gitelman syndrome. Children with chronic hypokalaemia associated with hypertension and elevated urine potassium and chloride most likely have Liddle syndrome or Apparent Mineralocorticoid Excess. Focused history, physical examination, especially volume status and spot urine chloride helps in the differential diagnosis these cases.

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AUTHORS' NOTE

KF Akl conceived the paper, oversaw data collection from medical records, conducted data analysis, wrote manuscript and approved final version. JH Albaramki participated in study design, medical record review, data analysis, and interpretation, critically revised the manuscript and approved the final version.

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