Distal renal tubular acidosis with severe hypokalaemia, probably caused by colonic $H^+-K^+-ATPase$ deficiency

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Abstract

We describe a 21 month old male infant who presented with failure to thrive associated with severe hypokalaemia and metabolic acidosis, together with hypomagnesaemia. Evaluation revealed marked renal and probable faecal potassium wasting, distal renal tubular acidosis, mild urinary magnesium wasting, and a normal gastric pH (gastric $H^+-K^+-ATPase$). Hypokalaemic forms of metabolic acidosis, such as diabetic ketoacidosis and proximal renal tubular acidosis were ruled out from the clinical picture. The hypokalaemia of distal renal tubular acidosis usually improves with alkali therapy, but this was not observed: despite correction of acidosis with 5 mmol/kg potassium citrate per day, an additional 5 mmol/kg potassium chloride was required to bring serum potassium to 3.5 mmol/l. At 3 years of age potassium was provided in the absence of potential alkali and acidosis ensued; serum bicarbonate fell to 10 mmol/l. Although a specific genetic analysis is not yet possible, the abnormalities are consistent with a novel form of distal renal tubular acidosis. The pathophysiology probably does not stem from defects in the vacuolar $H^+-ATPase$ but more likely from deficient activity of the colonic isoform of $H^+-K^+-ATPase$ that is resident in the medullary collecting duct and mediates potassium absorption and proton secretion.

(Arch Dis Child 2001;84:504–507)

Keywords: metabolic acidosis; renal tubular acidosis; hypokalaemia; hypomagnesaemia; kaliuresis; $H^+-K^+-ATPase$

Potassium homeostasis depends on both the kidneys and colon, which respond to dietary intake, to adjust the rates of potassium secretion and absorption. Potassium is absorbed in the renal outer medullary collecting duct and in the distal colon. Potassium absorption is mediated at these sites by an $H^+,K^+-ATPase$ (HKA) pump, which is a member of the P type family of cation transport ATPases. Such a pump forms a phosphorylated intermediate, is inhibited by vanadate, and mediates the absorption of potassium and the secretion of protons.^{1,2} There are at least two isoforms of HKA: one occurs in gastric parietal cells, and is responsible for secreting acid into the stomach; and the other is the colonic $H^+,K^+-ATPase$ (cHKA). The cHKA is

found in apical membranes of colonic epithelial cells and kidney medullary collecting duct.³ The colonic isoform is normally expressed at high levels in the colon and lower levels in the kidney. Its activity, however, is sharply induced in the outer medullary collecting ducts in the kidney when animals are maintained on a potassium deplete diet,^{3,4} suggesting that cHKA may play an important role in potassium homeostasis.¹ Studies of cHKA deficient mice given potassium deficient diets⁵ indicate that excess faecal loss of potassium leads to diminished plasma and muscle potassium compared to wild type mice. There are no published reports in the literature describing cHKA deficiency in humans.

Case report

An 11 week old male infant presented with a two week history of nasal congestion, mild cough, and poor feeding. There was no associated fever, breathing difficulties, rash, or change in stools. The baby was noted to have occasional small amounts of spitting, but no episodes of forceful vomiting or large amounts of emesis. He was healthy prior to presentation, born at 37 weeks gestation, with a birth weight of 2.98 kg (25th percentile). He received two days of phototherapy for hyperbilirubinaemia, and was noted to have mild hypospadias. He had been feeding and growing appropriately on cow's milk based formula with iron at his two month well child visit.

The baby was seen by his paediatrician on the day of admission. He appeared dehydrated and a 300 g weight loss was noted over the preceding three weeks. He was sent to the emergency room for further evaluation.

On physical examination, his temperature was 37.5°C rectally with a heart rate of 120 beats per minute, respiratory rate of 40 per minute, and blood pressure of 74/45 mm Hg. His weight was 3.65 kg (<5th percentile). He was alert, had a weak cry with no tears, sunken fontanelles, and dry skin with decreased turgor. The remainder of the examination was unremarkable.

Laboratory studies revealed severe hypokalaemia and acidosis with mild renal insufficiency (table 1). Anion gap was calculated at 18 mmol/l. White cell count was $13.2 \times 10^9/l$ with 48% segmented neutrophils and 48% lymphocytes; packed cell volume was 0.32. Urinalysis showed pH 8, 2+ protein, 2+ haemoglobin, negative leucocyte esterase, and 0–5 white blood cells per high power field. Blood and urine cultures were sterile.

After two 20 ml/kg boluses of normal saline, he was rehydrated with 5% dextrose and 34

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Accepted 8 February 2001

Table 1 Results of serum chemistry

Age	Condition	Na	K	Cl	HCO ₃	BUN	Creatinine	Glucose	Ca	Mg
77 days (HD 1)	Dehydrated	133	1.9	102	13	8.9	71	5	2.6	1.0
78 days (HD 2)	Dehydrated	140	1.5	116	9	5.7	62	7.1	2.9	0.5
84 days (HD 8)	Seizure	142	3.9	118	15	1.1	44	4.6	—	0.5
3.1 years	Well on therapy	140	3.4	99	26	2.9	35	3.8	2.6	0.5
3.3 years	Acidotic off alkali	139	4.4	109	10	2.9	35	4.4	2.8	0.6

All results given in mmol/l.
HD, hospital day.

mmol/l NaCl plus 20 mmol/l KCl at a rate twice that of his maintenance needs. He had several episodes of rust coloured emesis overnight, and had a large urine output of 10 ml/kg/h. The following morning, examination noted decreased alertness, with a decreased response to pain and less spontaneous movement. He was still dehydrated, with sunken fontanelles and sluggish pupils. Morning laboratory studies had worsened, particularly with respect to hypokalaemia and acidosis (see table 1). Serum magnesium was also reduced. Spot urine revealed a fractional excretion of potassium of 70%. An electrocardiogram showed a prolonged QT and possible U waves. He was then transferred to the paediatric intensive care unit for cardiac monitoring, electrolyte replacement, fluid resuscitation, and serial blood chemistry evaluations. A nasogastric tube and right subclavian line were placed.

Initially, he required large amounts of intravenous potassium, magnesium, and sodium bicarbonate to correct a persistent hypokalaemic and hypomagnesaemic metabolic acidosis; subsequently he was maintained on oral KCl and potassium citrate. Urinary potassium losses remained inappropriately high (fractional excretion of potassium ranged from 70% to 113%) despite the low serum potassium. Serum aldosterone was within the normal range.

A six hour urine had a volume of 70 ml (2.6 ml/kg/h) with a 24 hour projection of 28 mmol potassium (6.6 mmol/kg/day), 6 mmol sodium (1.4 mmol/kg/day), 2.2 mmol magnesium (0.5 mmol/kg/day), and 14 mmol chloride (3.2 mmol/kg/day); calcium was less than 1 mmol (<0.23 mmol/kg/day). Creatinine clearance on this specimen was 57 ml/min/1.73 m². Fractional excretions were: potassium 114%; sodium 0.5%; chloride 1.1%; magnesium 9.8%. Urine anion gap values were consistently greater than +10 mmol/l and urine pH values consistently 7 or higher, ruling out significant distal acidification or ammonia excretion. A urine minus blood pCO₂ value was less than 20 mm Hg, supporting a distal acidifying defect.⁶ Apart from some mild bicarbonate wasting, most proximal tubular functions were normal, including a lack of glycosuria, aminoaciduria, or phosphate wasting (tubular reabsorption of phosphate was 83%).

His hospital course was complicated by seizure activity on hospital day 8, consisting of rhythmic eye movements with gaze deviated to the right, head bobbing, and yawning. The episode lasted approximately seven minutes and was relieved with lorazepam. Laboratory studies at this time revealed only hypomagnesaemia (see table 1). He was started on oral magnesium therapy. Computed tomography of the

head showed normal lobar formations, symmetric ventricular system, and minimal air in the left mastoid. Magnetic resonance imaging of the brain showed a thrombosed lateral sinus and deeper vein on the left, and no significant brain parenchymal changes. Electroencephalogram was normal. An evaluation of his coagulation status was unrevealing, and the thrombosis was felt to be a result of severe dehydration.

Because of mild diarrhoea, stool electrolytes were measured on hospital day 18. The results showed: pH 5.5, bicarbonate <5 mmol/l, Na 51 mmol/l, K 53.4 mmol/l, Cl <1 mmol/l, phosphorus <0.2 mmol/l, Mg 19.2 mmol/l. These data were consistent with poor gastrointestinal conservation of potassium and magnesium, despite gross deficits in these electrolytes.

Renal ultrasound showed grade II bilateral hydronephrosis with excellent parenchymal preservation and no evidence of obstruction. Kidney size was approximately 6 cm bilaterally with 5 mm of hydronephrosis on the left and 7 mm on the right, as measured from the anterior to posterior views. The ureters were dilated on the right distally and on the left proximally. A voiding cystourethrogram showed no reflux. A repeat renal ultrasound on hospital day 22 showed echogenic kidneys consistent with medical renal disease, felt to be a result of acute renal failure and dehydration. The hydronephrosis had improved, the ureteral dilatation had resolved, and there was no nephrocalcinosis. The urine dipped positive for blood and protein early on, but this gradually improved and resolved.

The patient was discharged home on hospital day 25 on potassium citrate 20 mmol, potassium chloride 20 mmol, and magnesium oxide 2.5 mmol per day. The estimated total dose of potassium was 10 mmol/kg/day, while the estimated dose of potential alkali was 5 mmol/kg/day. The magnesium replacement computed to 60 mg (2.5 mmol) elemental Mg per day, which exceeds recommended dietary allowance.

At a recent follow up visit, now three years after his hospital discharge, he was just below the 5th percentiles for height and weight on a daily regimen of potassium chloride 60 mmol, potassium citrate 30 mmol, and magnesium oxide 12 mmol. These doses computed to a total daily dose of 7.5 mmol/kg potassium, 2.5 mmol/kg potential alkali, and 289 mg (12 mmol) elemental Mg per day, which greatly exceed recommended dietary allowances. Serum chemistry at this time revealed mild hypokalaemia and moderate hypomagnesaemia (see table 1). Anion gap was 15 mmol/l. The estimated glomerular filtration rate (Schwartz formula^{7,8}) was normal at

124 ml/min/1.73 m². The fractional urinary excretion of potassium was 50%, which is high for the serum concentration of potassium. A screening hearing test did not reveal any deafness.

To test whether severe hypokalaemia alone was responsible for the acidosis,⁹ we stopped the potassium citrate for one week, while the daily dose of potassium chloride was commensurately increased to maintain comparable potassium replacement. The parents noted that he became irritable and agitated, and laboratory results confirmed that he had become severely acidotic despite normal potassium concentrations (see table 1); anion gap was 20 mmol/l. The venous blood pH was 7.25, pCO₂ 26 mm Hg, and base excess -15 mmol/l.

To rule out a deficiency of the gastric H⁺-K⁺-ATPase isoform, the patient was evaluated for the ability to acidify gastric contents. A pH probe measured a gastric pH of 1.1, confirming the presence of gastric H⁺-K⁺-ATPase activity.

Discussion

Potassium depletion is common in patients with metabolic acidosis, as a result of gastrointestinal and/or renal losses of potassium.^{10 11} However, the initial serum potassium concentration is frequently normal as a result of cellular buffering of protons with shifts of potassium out of cells. Similar effects may occur with diabetic ketoacidosis, in which the insulin deficiency plus the hyperglycaemia promote potassium movement into the extracellular fluid. Indeed, when hypokalaemia initially presents with metabolic acidosis, there is a very severe potassium deficit, and correction of the acidosis results in further reduction in serum potassium concentrations. Such was the case in our patient; he required 15 mmol/kg potassium intravenously at presentation and more subsequently.

Our patient did not present with excessive gastrointestinal secretions (diarrhoea, laxative abuse), salt wasting nephropathy, or ketoacidosis (the major hypokalaemic states associated with metabolic acidosis). However, the anion gap was slightly increased on most determinations, but we were unable to show the presence of lactic acidosis, ketoacidosis, renal failure, drug ingestion, or massive rhabdomyolysis.¹¹ Urine amino acids and organic acids were normal at 1.3 years of age. However, our patient has recently shown slightly increased serum albumin values (51–54 g/l), which can raise the anion gap.¹¹

Most cases of distal renal tubular acidosis have hypokalaemia, because the impairment in the H⁺-ATPase pump results in more potassium secretion in the cortical collecting duct^{11–13}; they have hypokalaemia at the time of diagnosis.^{14 15} In addition, metabolic acidosis will diminish net proximal fluid reabsorption,¹⁶ leading to increased distal salt delivery and secondary hyperaldosteronism with increased urinary potassium losses. Indeed, hypokalaemic periodic paralysis is seen with the renal tubular acidosis associated with Sjögren syndrome.¹⁷ Many cases of autosomal recessive distal renal tubular acidosis have been shown to

be a result of a defect in the B1 subunit of vacuolar H⁺-ATPase responsible for proton secretion in the distal nephron¹³; some of these patients also have sensorineural hearing loss, while others do not.¹⁴ Our patient does not have any detectable hearing loss.

In general, most urinary potassium wasting in metabolic acidosis is reversed by correction of the acidemia; however, in those patients with impaired activity of the H⁺-ATPase, hypokalaemia may persist because of secondary hyperaldosteronism and the secretion of excessive amounts of potassium in exchange for sodium reabsorption in the cortical collecting duct.^{13 18} Indeed, urine potassium values exceeded 80 mmol/l in adults with distal renal tubular acidosis when serum potassium values were in the 3.2–3.8 mmol/l range¹⁸; in absolute terms that corresponded to around 50 mmol potassium excreted in the urine per day or less than 1 mmol/kg/day. Most children with distal renal tubular acidosis are adequately treated with mixtures of sodium and potassium citrate¹³ and do not require additional potassium. Our patient continued to excrete 50% of his filtered urinary potassium despite correction of the acidosis, and his serum aldosterone concentration was not increased; this extrapolated to a daily potassium excretion of about 170 mmol/day or 14 mmol/kg/day. This large urinary loss of potassium suggested a defect in the activity of the second proton pump in the collecting duct, the HKA pump that secretes protons and also reabsorbs potassium. Indeed, vanadate, an inhibitor of the HKA, when administered to rats caused inappropriate urinary potassium wasting and hypokalaemia, as well as metabolic acidosis.¹⁹

The cause of the hypomagnesaemia in this patient is not clear; however, this disturbance is frequently associated with hypokalaemia.²⁰ Concurrent magnesium and potassium depletion may be seen in cases of secondary hyperaldosteronism, prolonged intravenous therapy without magnesium supplementation, and with chronic gastrointestinal losses. In addition, systemic acidosis is often associated with renal magnesium wasting.^{21–23} Our patient may have had each of these clinical problems during the initial presentation, but the hypomagnesaemia has persisted for more than three years, in the absence of hypercalciuria and nephrocalcinosis.^{24 25} Normally, about 5% of filtered magnesium is excreted in the urine,²⁶ and this amount decreases with magnesium depletion.²⁷ While our patient excreted about 10% of filtered magnesium, the ratio of urine magnesium to creatinine (mol/mol) ranged between 1.1 and 1.8, which was not high for age,²⁸ but might be inappropriately high in the setting of hypomagnesaemia. Perhaps the chronic hypokalaemia inhibited magnesium transport in the thick ascending limb of Henle's loop.²⁶ In addition, there may be excessive stool losses of magnesium which have not been quantified.

Immunocytochemistry using an antibody to cHKA reveals apical localisation of signal in the majority of cells in the outer medullary collecting duct, characteristic of principal cells, as well

as in apical membranes of colonic surface epithelium.³ Potassium depletion resulted in an increase in expression of cHKA mRNA or protein in cells of the medullary collecting duct but not in the colon,^{4-5,29} suggesting that cHKA may play an important role in potassium homeostasis in the kidney, particularly during times of potassium depletion. Although there was no regulation of cHKA mRNA or protein in rats with chronic metabolic acidosis,⁴⁻²⁹ this does not exclude a role of cHKA in mediating some distal nephron H⁺ secretion in humans.

The role of the cHKA isoform in vivo has been further outlined in a mouse model, employing a targeted disruption of the corresponding gene.¹ The ability of wild type and homozygous mutants to conserve potassium in the colon and kidney was analysed under normal and potassium depleted conditions. The most significant finding was that the mutant mice (cHKA ^{-/-}) became severely hypokalaemic relative to wild type mice (cHKA ^{+/+}) during potassium deprivation, suggesting that cHKA plays an important role in potassium homeostasis. In addition the cHKA ^{-/-} mice lost twice as much weight and more muscle potassium than did cHKA ^{+/+} mice during potassium depletion; the excessive loss of potassium was in the stool, not in the urine. As no parameters of acid-base or magnesium homeostasis were measured, it was impossible to know whether these mutant mice resemble the patient we have just described. Furthermore, as potassium depletion results in an increased signal for cHKA in the renal outer medullary collecting duct,⁴⁻²⁹ it is surprising that the mutant mice did not have increased urinary potassium excretion during potassium deprivation.⁵ Perhaps there are differences between the knock out of cHKA in mouse and defective activity in man.

The child described in this report had distal renal tubular acidosis with urinary and faecal potassium excretion that was inappropriately high given his persistently low serum potassium measurements. He required potassium supplements well above the amount of potassium citrate that corrected his acidosis. When deprived of potassium citrate, this patient quickly became acidotic despite a normal potassium concentration. This metabolic acidosis occurred independent of the serum potassium concentration, and suggests that hypokalaemia was neither the cause nor a necessary condition for acidosis to occur.¹⁻⁹ His ability to acidify gastric contents and maintain a low gastric pH was confirmed, implying that he had a functional gastric HKA isoform. This patient's inappropriate urinary and faecal potassium wasting and his propensity towards metabolic acidosis, however, suggests that he has negligible cHKA activity. This may be a result of a functional defect or may be from actual cHKA deficiency caused by disruption of the corresponding gene. Currently, there is no gene probe or antibody available to confirm suspected cases of cHKA deficiency in human subjects.

Support for GJS was provided in part by NIH grant DK 50603.

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