

Hyperammonaemia with distal renal tubular acidosis

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Abstract

The case is reported of an infant with hyperammonaemia secondary to severe distal renal tubular acidosis. A clinical association between increased concentrations of ammonia in serum and renal tubular acidosis has not previously been described. In response to acidosis the infant's kidneys presumably increased ammonia synthesis but did not excrete ammonia, resulting in hyperammonaemia. The patient showed poor feeding, frequent vomiting, and failure to thrive, but did not have an inborn error of metabolism. This case report should alert doctors to consider renal tubular acidosis in the differential diagnosis of severely ill infants with metabolic acidosis and hyperammonaemia.

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Hyperammonaemia with metabolic acidosis is often observed in patients with inborn errors of metabolism, such as abnormalities of the urea cycle or organic acidurias.¹ The latter are often associated with an increased anion gap. Non-genetic causes of hyperammonaemia include perinatal asphyxia, total parenteral nutrition, liver disease, methaemoglobinaemia, and urinary tract infections.² Hyperammonaemia has not been reported in renal tubular acidosis. We report the case of a patient with hyperammonaemia and metabolic acidosis who was found to have distal renal tubular acidosis; correction of the acidosis led to a decrease in blood ammonia to normal concentrations.

Case report

A white girl, aged 47 days, presented with a history of poor feeding and vomiting since shortly after birth. She was born at full term to a 25 year old gravida 2, para 1 woman who had no pregnancy, delivery, or perinatal complications. The infant's birth weight was 3680 g and she was discharged home at 2 days of age. She never breast fed well, had frequent regurgitation, and did not regain her birth weight. Numerous changes in formula milk were initiated without success and an upper gastrointestinal tract series at 3 weeks of age showed profuse gastro-oesophageal reflux. The infant was treated with cisapride without much improvement. The vomiting persisted and she subsequently developed difficulty in breathing. She presented to the emergency

department with gasping respiration and was admitted to the Children's Hospital at Strong for failure to thrive and a possible metabolic disorder.

On physical examination her temperature was 37.2°C rectally with a heart rate of 174 beats/minute, blood pressure of 92/60 mm Hg, and a respiratory rate of 42-48/minute. Her weight was 2.92 kg. She appeared mottled and cachectic, but not cyanotic, with Kussmaul respirations. Her anterior fontanelle was soft and sunken; the mucous membranes were dry. Her skin showed tenting without subcutaneous fat, and capillary refill was prolonged to approximately three seconds. The rest of the physical examination was normal.

A venous blood pH measurement in room air was 6.99 with a partial pressure of carbon dioxide (pCO₂) of 1.87 kPa and a calculated total carbon dioxide (tCO₂) of 3 mmol/l. Her blood chemistry showed sodium 141 mmol/l, potassium 6.0 mmol/l, chloride 118 mmol/l, bicarbonate 6 mmol/l, glucose 5.1 mmol/l, blood urea nitrogen 24.3 mmol/l, creatinine 80 µmol/l, calcium 3.30 mmol/l, phosphorus 3.00 µmol/l, and magnesium 1.20 mmol/l; the anion gap was 17 mmol/l. Liver enzymes and serum albumin were normal. There was no brown discoloration of the blood samples. Metabolic studies showed that lactate was 1.3 mmol/l (normal 0.7-2.1 mmol/l) and pyruvate was 100 µmol/l (normal 30-80 µmol/l); however, there was an increased serum ammonia concentration of 144 µmol/l (normal 9-33 µmol/l; Vitros AMON slides, Johnson & Johnson, Rochester, NY). The white cell count was 46.5 × 10⁹/l with 38% neutrophils, 6% band forms, 45% lymphocytes, 10% monocytes, and 1% metamyelocytes; the packed cell volume was 0.37 and platelet count 890 × 10⁹/l.

Her cerebrospinal fluid was normal. Urine analysis gave a pH of 7.0, with negative glucose, protein, and ketones, moderate blood and 2+ leucocyte esterase; the microscopic examination showed 10-50 red blood cells/high power field and 10-50 white blood cells/high power field. The urine anion gap was +20 mmol/l, indicating the lack of urinary ammonium excretion.³ Blood, urine, and cerebrospinal fluid cultures were obtained and subsequently found to be sterile.

The infant was resuscitated with fluid with two 20 ml/kg boluses of normal saline followed by sodium bicarbonate, and she was treated with cefotaxime and gentamicin. The acidosis was initially poorly responsive to intravenous normal saline and sodium bicarbonate; indeed, with sodium bicarbonate and fluids she became

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Table 1 Serial measurements during treatment

Day	Ammonia	tCO ₂	pH of urine	HCO ₃ ⁻ /day	Arterial pH/pCO ₂ /pO ₂ /BE	Serum anion gap (mmol/l)	Serum creatinine (μmol/l)	Weight (kg)
1	144	6	7.0	28	7.29/1.6/19.6/-18	17	70.7	2.92
2	86	9	8.0	29	7.31/2.5/15.7/-15	14	53.0	3.15
3	52	19		35	7.51/3.7/14.5/0	16	44.2	3.40
4	25	23		27		10	44.2	3.40
5		24	8.0	18		11	44.2	3.50
10		18		18		13	35.4	
19		22	8.0	24		11	35.4	4.16

Day 1 is the first day of admission to hospital (47 days of age); ammonia in μmol/l in serum (normal 9–33); tCO₂ in mmol/l in serum; HCO₃⁻/day is daily supplement of bicarbonate plus acetate plus citrate in mmol; arterial pH/pCO₂ (kPa)/pO₂ (kPa)/BE, arterial values obtained from a radial artery catheter; and BE, base excess.

hypokalaemic. The acidosis began to improve after the addition of intravenous potassium acetate (total daily bicarbonate equivalents were about 9 mmol/kg; see table 1). Potassium citrate (Polycitra-K, Baker Norton Pharmaceuticals) by mouth was added the next day and the serum bicarbonates normalised over the next few days (table 1). The increased serum anion gaps decreased to the normal range as renal function improved. Concomitant with the correction of the acidosis, the hyperammonaemia resolved (table 1).

Urinary flow rates, initially high at 4.4 ml/kg/hour, increased to 8.9 ml/kg/hour on the second hospital day before gradually decreasing. Her urinary pH remained greater than 7.0 throughout her stay in hospital (table 1). An ultrasound examination showed bilaterally enlarged kidneys with severe hyperechoic medullary pyramids and shadowing compatible with medullary nephrocalcinosis (fig 1). Spot urine calcium to creatinine ratios after stabilisation were consistently less than 0.45 mol/mol (0.16 mg/mg) (normal <0.56 mol/mol (<0.2 mg/mg)). Additional metabolic evaluation showed no significant abnormalities of plasma amino acids, urine amino acids, or urine organic acids, with the exceptions of a slight increase in urinary lactate concentration and

low plasma alanine (97 fluid μmol/l; normal 205–532 μmol/l).

After resolution of the acidosis, the hospital course was complicated by a generalised tonic-clonic seizure that occurred in the presence of a serum magnesium level of 0.4 mmol/l, which was felt to be due to poor feeding plus massive urinary electrolyte losses. Electroencephalography and a head computed tomography were normal. The hypomagnesaemia corrected after magnesium sulphate supplements were added.

The patient was discharged home on day 7 (54 days of age) while receiving Polycitra-K (18 mmol/day or 5.3 mmol/kg/day). Because her serum bicarbonate concentrations had decreased to 18 mmol/l on day 10, Polycitra-K was increased to 24 mmol/day (7 mmol/kg/day). She was seen in our clinic 19 days after admission to the hospital (66 days of age); she was feeding well, having gained 1.24 kg since admission. Her gastro-oesophageal reflux resolved without cisapride and no seizure occurred while magnesium sulphate treatment was tapered. Her serum bicarbonate concentration was 22 mmol/l, with sodium 136 mmol/l, potassium 4.8 mmol/l, chloride 103 mmol/l, blood urea nitrogen 3.0 mmol/l, creatinine 35 μmol/l, calcium 2.64 mmol/l, phosphorus 2.25 mmol/l, and magnesium 0.70 mmol/l (all normal for age).

Follow up at 7 months of age showed an apparently healthy infant in the 50th centile for height and weight. Her serum bicarbonate concentration was 24 mmol/l while receiving 30 mmol/day Polycitra-K (3.7 mmol/kg/day). An hour after the alkali was given her urine pCO₂ was 4.67 kPa compared with a venous pCO₂ of 5.20 kPa, indicating a proton secretory defect of classic distal renal tubular acidosis.⁴⁻⁶

Discussion

Infants with a serious illness may have non-specific clinical symptoms and physical findings limited to failure to thrive, dehydration, vomiting, and lethargy. Infants with severe renal tubular acidosis can present with signs and symptoms that may mimic those observed with infection, cardiac disease, gastrointestinal problems, central nervous system defects, and inborn errors of metabolism. An appropriate approach to screening for the possibility of an inborn error of metabolism is to measure serum ammonia, lactate, and pyruvate, and to determine urinary amino and organic acid excretion.¹ Our patient had moderate



Figure 1 Renal ultrasound of the infant's right kidney showing markedly increased echogenicity of the medullary pyramids with shadowing, compatible with medullary nephrocalcinosis. The kidney was also mildly and diffusely enlarged, measuring 5.8 cm in length.

hyperammonaemia and was first evaluated for an inborn error of metabolism. Hyperammonaemia can be seen with urea cycle defects, fatty acid oxidation defects, and some organic acidurias, and may be seen transiently in newborn infants.^{1,7} Our patient had normal blood concentrations of glucose, lactate, pyruvate, and amino acids, and excreted in her urine no unusual amounts of ketones, amino acids, or organic acids, making a metabolic disorder highly unlikely.

Liver disease was ruled out by the normal serum albumin, bilirubin, and liver enzymes, plus the finding of a high blood urea nitrogen in the face of hyperammonaemia; the latter implicates, if anything, an active urea cycle. Methaemoglobinaemia, which has been associated with probable renal tubular acidosis,⁸ was considered unlikely in view of the absence of cyanosis or brown discoloration of the blood.

The low rate of urinary excretion of ammonia that occurs with distal renal tubular acidosis has been well documented,⁴ but hyperammonaemia has not previously been reported. It is well known that ammonia excretion by the kidneys increases markedly in response to metabolic acidosis.⁹⁻¹¹ Increased ammoniogenesis results from the induction of phosphate dependent glutaminase and glutamate dehydrogenase in the kidney.¹¹⁻¹³ Glutaminase catalyses glutamine to glutamate plus ammonia, whereas glutamate dehydrogenase converts glutamate to α -ketoglutarate plus ammonia. The increase in renal ammonia production occurs primarily at the level of the S1 and S2 segments of the proximal tubules.^{10,14} Some studies indicate that there are at least two phases to the renal ammoniogenic response to acidosis. There is an initial increase in ammonium excretion that precedes changes in enzymatic activity, which is followed by a sustained multifold increase in renal ammoniogenic enzyme activities.^{13,15,16} Acidosis does not appear to affect the liver's production of ammonia.¹⁷

Our patient most probably had distal renal tubular acidosis because she did not acidify her urine to less than pH 7.0 or excrete urinary ammonium despite severe metabolic acidosis. Under conditions of alkali loading she did not generate a urine to blood pCO₂ gradient, indicating that she probably had a secretory defect due to a deficiency in the number or function of proton pumps on the luminal membranes of medullary collecting duct cells.^{4,9} Decreased distal sodium delivery¹⁸ as a cause of distal renal tubular acidosis was ruled out by the high urinary flows and high urinary sodium concentration on the first day (86 mmol/l). She was also a poor feeder, with frequent vomiting, dehydration, failure to thrive, polyuria, and severe medullary nephrocalcinosis (fig 1), all characteristics of primary or classic distal tubular acidosis.^{4,6,19,20}

The nephrocalcinosis probably resulted from chronic acidosis with bone buffering leading to increased calcium release from bone with hypercalcaemia and hypercalciuria,²¹ decreased calcium solubility in her alkaline urine,^{4,9} and a decreased excretion of urinary

citrate, an important factor in solubilising urinary calcium.^{4,12} Correction of the acidosis by day 5 was associated with normocalciuria (urine calcium to creatinine ratio of 0.31 mol/mol (0.11 mg/mg)). The polyuria resulted from the medullary nephrocalcinosis, potassium depletion, salt loading, and transient renal insufficiency. The hypokalaemia probably resulted from chronic poor feeding, vomiting, and sodium loading during the fluid resuscitation. The hyperphosphataemia might have been due to acidosis leading to bone resorption combined with renal insufficiency. The initially increased anion gap was probably due to this renal insufficiency. The vomiting, poor feeding, and failure to thrive, though non-specific, may have resulted from the severe acidosis and probably contributed to the low plasma alanine and hypomagnesaemia.

We believe that increased renal ammonia synthesis in the presence of distal renal tubular acidosis led to a lack of ammonia diffusion trapping as NH₄⁺ in the urine,¹¹ impaired ammonia excretion,^{4,12} back diffusion of ammonia into the renal medullary interstitium, a failure to reverse the acidosis, and accumulation of ammonia in the blood. Indeed, the hyperammonaemia observed in this patient led the doctors to initially investigate an inborn error of metabolism. The fact that our patient consistently showed urine pH values greater than 7.0 indicates that much less of the ammonia newly synthesised in the proximal tubule would be excreted in the urine. With correction of the acidosis by exogenous alkali, the stimulus for ammonia synthesis was decreased¹⁰ and its blood concentrations fell. In other infants with less severe distal renal tubular acidosis, in whom the minimum urinary pH is lower than that of our patient, substantially more synthesised ammonia would be trapped in the urine and excreted; hyperammonaemia might then be a less obvious finding.

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