

Failure to thrive and nephrolithiasis in a boy with congenital cyanotic heart anomaly—questions

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Case summary

A 3-year-old boy from Kosovo was referred to us for evaluation of failure to thrive and an episode of macro-

scopic hematuria. He was the son of healthy non-consanguineous parents. His past medical history was notable as he had been born with a cyanogenic heart anomaly (truncus arteriosus communis) which had been treated medically with furosemide and captopril until successful cardiac surgery, performed at 2 years of age. Following cardiac surgery, echocardiography with Doppler studies confirmed a successful repair, with no mixing of the arterial and venous blood. His cyanosis resolved and medical treatment was discontinued. Despite this apparently good outcome, he failed to thrive.

Upon admission to our unit, the boy was tachypneic, dehydrated and listless, with significant growth retardation [height 80 cm (−4.5 SD; weight 9.0 kg (−4.9 SD)]. There was no cyanosis. Cardiac examination revealed a systolic murmur, grade III/IV, at the precordium. Ultrasound of the abdomen revealed no hepatosplenomegaly, and both kidneys were of normal size without dilatation of the pelvicaliceal system. A single non-obstructive stone measuring 10 mm was seen in the lower pole of the left kidney (Fig. 1) without evidence of generalized nephrocalcinosis. A repeat echocardiogram confirmed adequate repair of the cyanotic anomaly.

Laboratory investigations included a full blood count, revealing: hemoglobin 13.4 g/dl, erythrocytes $4.66 \times 10^{12}/l$, leukocytes $8.6 \times 10^9/l$, hematocrit 42.7 vol%, platelets $344 \times 10^{11}/l$. The results of the arterial blood gas analysis were: pH 7.12, pCO₂ 2.45 kPa, pO₂ 12.7 kPa, O₂ saturation 98%. Serum electrolytes and liver and bone biochemistry test results were: HCO₃ 10.1 mmol/l, urea 4.1 mmol/l, creatinine 9 μmol/l, uric acid 116 μmol/l, Na 145 mmol/l, K 3.3 mmol/l, Ca 2.23 mmol/l, P 0.74 mmol/l, Mg 1.0 mmol/l, Cl 115 mmol/l, alkaline phosphatase 762 U/l, parathyroid hormone 33.3 pg/ml (normal 10–65), glycemia 4.6 mmol/l, total protein 78 g/l,

The answers to these questions can be found at <http://dx.doi.org/10.1007/s00467-011-1790-4>.

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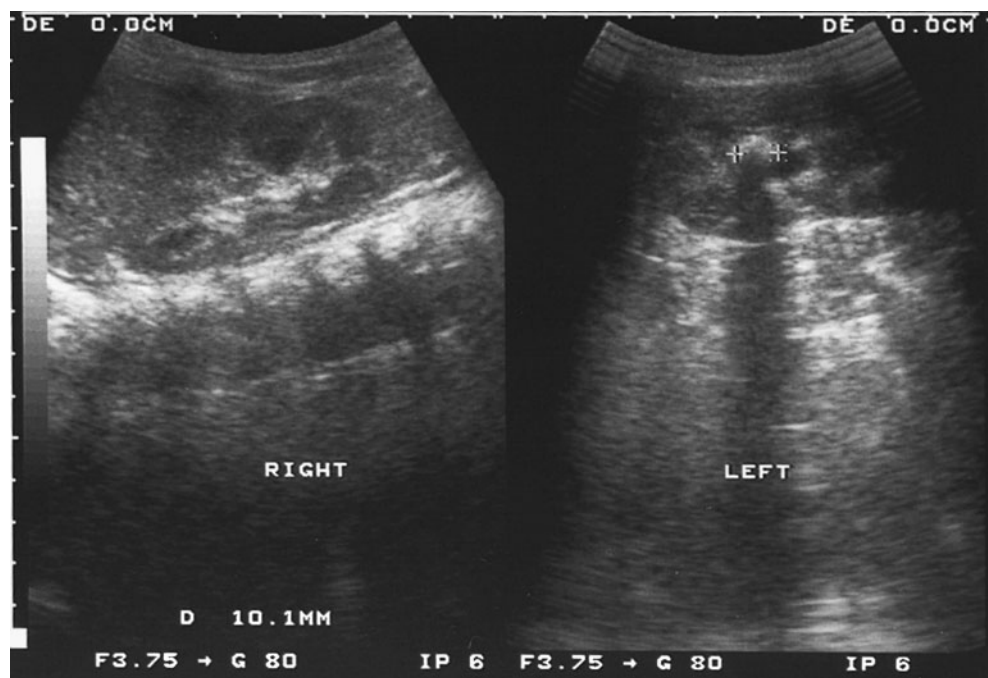
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Fig. 1 Non-obstructive calculus in the left kidney



albumin 49 g/l, bilirubin 7 $\mu\text{mol/l}$, aspartate aminotransferase 32 U/l, alanine aminotransferase 17 U/l, glutamic oxaloacetic transaminase 26 U/l, lactate dehydrogenase 570 U/l, creatine phosphokinase 20 U/l.

The spot urine examination revealed: protein 2+ (1.07 g/l, electrophoresis of urinary proteins showed complete tubular proteinuria), blood 1+, pH 7.17 (with electrode). Urinary electrolytes were as follows: Na 58 mmol/l, K 37 mmol/l, Cl 56 mmol/l. The urinary calcium:creatinine ratio was elevated at 1.82 mmol/mmol (normal <0.70). Tubular reabsorption of phosphate and uric acid was 70 and 78%, respectively. The nitroprusside reaction for urinary cystine was negative. The urinary oxalate:creatinine ratio was 215 mmol/mol (normal 35–126), urinary citrate:creatinine ratio was 80 mmol/mol (normal 150–1007), urinary glycolate:creatinine ratio was 24 mmol/mol (normal 17–103), and urinary glycerate was non-detectable. There was a generalized hyperaminoaciduria.

In addition to the above clinical findings, the findings of an ophthalmological examination were normal, and audiological examinations excluded any sensorineural deafness. The patient was treated with oral potassium and alkali supplementation (K-citrate 10 mmol/day+NaHCO₃ 20 mmol/day). At review 3 months later, the acid–base status, serum phosphate and uric acid had normalized as had the urinary excretion of proteins, oxalate, citrate, amino acids, calcium, phosphate and uric acid.

Questions

1. What is diagnosis of his tubular dysfunction?
2. What is the link between a cyanotic heart anomaly, failure to thrive and nephrolithiasis?
3. What is the explanation for the proximal renal tubular abnormalities?

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Answers

1. Distal (Type I) renal tubular acidosis (RTA).

This child had biochemical evidence of hyperchloremic metabolic acidosis with a normal serum anion gap

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$([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$. Simultaneous to blood chemistry, urinalysis revealed pH of 7.17, indicating a distal tubular acidification defect. The urinary anion gap $[Na^+] + [K^+] - [Cl^-]$ was positive at 39 mmol/l, suggesting a low urinary NH_4^+ in favor of RTA.

- Cyanotic heart anomaly leads to a respiratory metabolic acidosis (due to retained CO_2) and failure to thrive. Successful repair of the heart anomaly should result in prompt resolution of cyanosis and metabolic acidosis (within 48 h) [1]. Persistence of metabolic acidosis beyond this period and continued failure to thrive should alert the clinician to an alternative (extra-cardiorespiratory) cause, such as a renal tubular acidification defect, as in this case.
- The findings of low molecular weight proteinuria, aminoaciduria, phosphaturia, and uricosuria alongside metabolic acidosis may lead to confusion with renal Fanconi syndrome. These proximal tubular abnormalities were transitory and resolved with alkali therapy. Transitory proximal renal tubular dysfunction may be associated with distal RTA [2–4].

Commentary

It has been well established that chronic cyanosis in children with congenital heart anomalies may affect glomerular structure and function, leading to glomerulopathy, manifesting with proteinuria [5–7]. Krull et al. investigated 27 children with non-repaired congenital cyanotic heart disease over a range of ages, from 1-day-old infants up to adults, 25 years of age [6]. Significant proteinuria was found in 12 patients (mainly the glomerular

type), but only in 1 out of 10 children younger than 10 years of age. In this case, our patient had significant proteinuria, of a tubular pattern that was transitory, excluding the possibility of progressive glomerular disease.

There are very few studies on the renal tubular function of children with cyanotic heart diseases. Burlet et al. investigated 18 pediatric patients aged 1.8–14.6 years and found that the majority had mild to moderate metabolic acidosis due to reduced proximal tubular threshold for bicarbonate reabsorption (type 2 RTA) [8]. Rodriguez-Soriano et al. reported a 9-year-old girl with tetralogy of Fallot [9]. A titration study revealed that her metabolic acidosis was of proximal tubular origin, due to a low bicarbonate threshold (18 mmol/l), whilst distal acidification of urine was preserved. After successful cardiac surgery, the patient's acid base status and proximal tubular bicarbonate reabsorption both normalized. Vida et al. studied 73 patients with cyanotic heart diseases and found 56 patients with metabolic acidosis [1]. Forty-eight patients had normal anion gap metabolic acidosis. According to the findings of the urinary anion gap measurements, 39 patients had secondary distal RTA (81%), whilst 9 patients had proximal RTA (19%). The most noteworthy finding from this study was the fact that 10 patients, with congenital cyanotic heart anomaly and secondary RTA, had normalized metabolic acidosis within 48 h of successful cardiac surgery.

Our case illustrates that postoperatively, despite successful cardiac surgery, failure to thrive was still evident. Only the acute presentation with a renal stone prompted further investigation of the child's metabolic status. Nephrolithiasis has been described in children with congenital cyanotic anomalies as an adverse effect of furosemide treatment for congestive heart failure [10, 11]. In the case we present, despite previous furosemide treatment, a renal ultrasound scan performed immediately before cardiac surgery showing no evidence of nephrocalcinosis or stones. Loop diuretics were not continued following surgery. We do not have precise data about the immediate postoperative acid base status in our patient. However, correction of cyanosis and a favorable echocardiographic result indicates successful cardiac repair. The presence of persistent failure to thrive in association with new renal stone disease prompted us to look for other metabolic causes.

Hyperchloremic metabolic acidosis with a normal serum anion gap, inappropriately high urinary pH, a positive urinary anion gap, and hypercalciuria indicated distal (type 1) RTA. In addition, our patient showed hypocitraturia, which is found in distal RTA and is a risk factor for nephrolithiasis/nephrocalcinosis. Citrate is a potent inhibitor of stone formation and exerts its effect through the formation of calcium–citrate complexes, which decrease the concentration of free calcium in urine, increase its solubility and prevent supersaturation [12, 13]. In the serum, citrate

exists as a divalent anion coupled with magnesium and calcium and is freely filtered through the glomerulus. In humans 60–90% of the filtered load is reabsorbed in the proximal tubule. Excretion of citrate is dependent on pH (systemic, intracellular, tubular), and in distal RTA daily excretion is usually less than 100 mg, thus increasing the risk of urolithiasis. Various factors may lead to hypocitraturia such as a low citrate diet, poor gastrointestinal absorption of citrate, low urinary potassium, and genetic factors. Besides beneficial effects in patients with distal RTA, there is evidence that treatment with potassium or magnesium citrate decreases the occurrence of new stones in hypocitraturic stone formers [13, 14].

Distal RTA may be primary or secondary. In childhood, secondary distal RTA is very rare and is usually associated with Sjögren's syndrome, systemic lupus erythematosus or drugs. These all seemed unlikely in our patient. We undertook a genetic analysis of H⁺-ATP-ase genes associated with autosomal recessive RTA (*ATP6V1B1* and *ATP6V0A4*) in the first instance, given an absence of family history of renal stones or acidosis. No mutations were detected in these genes and therefore we screened the *AE1* gene (*SLC4A1*), detecting a heterozygous mutation R589C. This mutation has been described in patients with autosomal dominant distal RTA [15–18]. Unfortunately, DNA for the genetic analysis of the child's parents was not available. We propose that this mutation was de novo since both parents were healthy. Consistent with this is the fact that codon 589 is considered to be a mutational hotspot in the *AE1* gene [19, 20].

Our patient also demonstrated significant metabolic/biochemical abnormalities of the proximal tubule, namely low molecular proteinuria, hypouricemia with hyperuricosuria, hypophosphatemia with hyperphosphaturia, and generalized hyperaminoaciduria. However, following oral alkali therapy, all these abnormalities normalized. Watanabe [2] and our group [3] have previously described transitory proximal tubular dysfunction in children with distal RTA. The most likely mechanism for proximal tubular dysfunction is long-lasting hypokalemia. Hypocitraturia and hypercalciuria in our case are explained by the metabolic acidosis, whereas the generalized aminoaciduria is not a normal feature of systemic acidosis and could be explained in concert with a generalized defect of the proximal tubule due to hypokalemia. In a study by Emery et al. 45% of patients with hypokalemia showed increased urinary excretion of β 2 microglobulin, which normalized with potassium supplementation [21].

In addition, hyperoxaluria has been reported in children with distal RTA [3, 4, 22]. The findings of normal urinary excretion of glycolate and glycerate and the resolution of hyperoxaluria with metabolic compensation, indicate the absence of a primary hyperoxaluria defect in our patient.

We conclude that cyanotic congenital heart anomalies often present with mild to moderate metabolic acidosis as a consequence of proximal or distal tubular dysfunction, in addition to any respiratory acidosis. Successful surgical heart repair should result in prompt resolution of metabolic acidosis. Persistence of metabolic acidosis following cardiac repair should alert the clinician to perform a cardiological re-evaluation and to look for additional causes of metabolic acidosis. Our patient presented with two causes of metabolic acidosis: a cyanotic congenital heart anomaly (truncus arteriosus communis) and autosomal dominant distal RTA as a result of an AE1 mutation. This second cause of metabolic acidosis contributed to a failure to thrive and renal stone disease.

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Conflict of interest None.

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