CASE REPORT

Transient Fanconi syndrome in two preterm infants with hydronephrosis and urinary tract infection

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Abstract Type IV renal tubular acidosis is known to occur in obstructive uropathy with urinary tract infection. Fanconi syndrome, however, has not been described in these settings. We report two preterm infants who developed Fanconi syndrome associated with hydronephrosis and urinary tract infection. Patient 1 is a boy with 21 trisomy, bilateral renal hypoplasia and bilateral vesicoureteral reflux delivered at 35 weeks' gestation. At postnatal day 42, he developed Fanconi syndrome after urinary tract infection, which persisted until the surgical correction of vesicoureteral reflux. Patient 2 was delivered at 35 weeks' gestation. At postnatal day 9, he was admitted for severe dehydration. He had phimosis and ultrasonography showed left pelviectasis. Laboratory data were compatible with Fanconi syndrome, which resolved spontaneously after fluid therapy. Subsequently urine culture grew bacteria and treatment for infection and topical corticosteroid for phimosis were performed. DMSA scintigraphy performed later showed left renal scar. Tubular cell stretch, due to vesicoureteral reflux in Patient 1 and phimosis in Patient 2, and urinary tract infection in association with immaturity of tubules are thought to have caused Fanconi syndrome.

Keywords Renal tubular acidosis · Proximal tubule · Cell stretch · Urinary tract obstruction · Immaturity

Introduction

Fanconi syndrome (FS) is a generalized dysfunction of proximal tubules leading to the urinary loss of phosphate, uric acid, glucose, amino acids, and low molecular weight proteins. In proximal cells, the electrochemical gradient generated by the basolateral $\text{Na}^+\text{-K}^+\text{-ATPase}$ facilitates the activity of sodium dependent co-transporters expressed at the apical side, allowing the reabsorption of glucose, phosphate, and others [1]. To maintain the electrochemical gradient, proximal cells have high metabolic rates and are rich in mitochondria. They also have endocytic receptors such as megalin and cubilin that are critical for the reabsorption of filtered proteins [2]. Thus, the mechanism of FS can be categorized as the inhibition of (1) $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity [1], (2) mitochondrial activity, and (3) receptor-mediated endocytosis.

Renal tubular acidosis has been reported in infants with obstructive uropathies and urinary tract infection (UTI) [3]. The type of renal tubular acidosis in these settings is type IV, and FS has rarely been described. We report here two infants with hydronephrosis and UTI who developed FS.

Case reports

Patient 1

The patient was delivered at 35 weeks' gestation via cesarean section for fetal distress. Apgar score was 2 at 5 min. Birth weight was 1970 g. He showed cyanosis with SPO_2 80%. Physical examinations revealed hypotonia, inner epicanthal folds, and low-set ears. Cardiac ultrasonography revealed tetralogy of Fallot. An abdominal X-ray showed double bubble sign, and an upper gastrointestinal series

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made the diagnosis of duodenal obstruction. A blood test showed serum creatinine 0.8 mg/dL, sodium 140.1 mmol/L, potassium 3.4 mmol/L, chloride 102 mmol/L, calcium 9.4 mg/dL, phosphorus 5.0 mg/dL, uric acid 5.7 mg/dL, and normal venous gas. Urinalysis showed protein 1+, blood $\pm$, and no cells or casts. Ultrasonography showed left hydronephrosis and hydroureter. Diamond-shaped anastomosis was performed on day 4. During the operation blood pressure decreased to 50 s/30 s mmHg. On postoperative day 1, serum creatinine increased to 1.6 mg/dL. Urinalysis showed granular casts with fractional excretion of sodium (FE_{Na}) of 3.7% indicating acute tubular necrosis. A peripheral blood karyotype returned as 47, XY+21.

On postnatal day 8, he became acidemic (venous pH 7.265, pCO_2 34.4 mmHg, bicarbonate 15.1 mmol/L, anion gap 15.7 mmol/L). Serum creatinine was 2.6 mg/dL, sodium 135 mmol/L, potassium 6.7 mmol/L, and chloride 105 mmol/L. Urine β_2 microglobulin was 26.09 mg/L (<0.2) and *N*-acetyl- β -D-glucosaminidase (NAG) 76.1 U/g creatinine (<5). Urine sodium was 31.0 mmol/L and FE_{Na} 8.1%. With sodium bicarbonate infusion, the venous pH and bicarbonate concentration normalized on the next day. He subsequently required bicarbonate of 3.5 mEq/kg per day. On postnatal day 15, he developed acute pyelonephritis caused by *Pseudomonas aeruginosa*. The infection resolved with amikacin for 7 days and piperacillin for 3 weeks. Voiding cystourethrogram (VCUG) revealed left grade IV and right grade III vesicoureteral reflux (VUR). On postnatal day 42, venous pH decreased to 7.185 with bicarbonate 11.6 mmol/L and anion gap 16.6. Urine pH was 5.71. Urinalysis showed protein 2+, glucose 1+, blood 1+, β_2 microglobulin 66.27 mg/L, and NAG/Cr 91.9 U/g. Serum creatinine was 1.0 mg/dL, Na 138.3 mmol/L, K 3.7 mmol/L, Cl 104 mmol/L, Ca 8.8 mg/dL, P 4.8 mg/dL, uric acid 4.0 mg/dL, glucose 97, tubular reabsorption of phosphate 52%, urine P/Cr 2.6 (95th percentile 5.24), fractional excretion of uric acid (FE_{UA}) 62%, urine uric acid/Cr 4.3 (<1.27). Panaminoaciduria was absent. Urine-to-blood dioxide gradient was 22.1 mmHg, and urine anion gap ranged from 15 to 30 mEq/L. He was diagnosed as having FS and distal RTA. At 3 months of age, repeated ultrasonography revealed bilateral renal hypoplasia and hydronephrosis. Cefaclor had been started after the diagnosis of VUR, but he had another episode of pyelonephritis due to *Pseudomonas aeruginosa* at 5 months of age, which was treated with piperacillin/tazobactam. Tc-99m dimercaptosuccinic acid (DMSA) scintigraphy revealed defects in the upper, middle and lower portion of the left kidney and the lower portion of the right kidney. Surgical correction of VUR was performed, and at 8 months of age, the venous pH was 7.377, pCO_2 36.6 mmHg, bicarbonate 21.0 mmol/L. Serum creatinine was 0.6 mg/dL, calcium 9.9 mg/dL, phosphorus 6.1 mg/dL, and uric acid

5.7 mg/dL. Urinalysis revealed pH 6.0, protein $\pm$, glucose $-$, blood $\pm$, and granular casts. Urine β_2 microglobulin was 20.97 mg/L, and NAG 73.4 U/g creatinine. Sodium bicarbonate was tapered and successfully discontinued.

Patient 2

The patient was delivered at 35 weeks' gestation with birth weight of 2670 g. Apgar score was 9 at 1 min. He was breastfed and had no history of diarrhea. His weight decreased continuously to 2206 g on day 9, and he was admitted. Body temperature was 36.9°C, heart rate 160 beats per min, respirations 49 per min, and blood pressure 92/61 mmHg. The color was dusky brown. The anterior fontanelle was slightly depressed. Ballooning of the foreskin during voiding was observed. The rest of the physical examination was unremarkable. The white blood cell count was 42,500/ μ L, the red cell count 5,100,000/ μ L, hematocrit 55.7%, hemoglobin 19.4 g/L, and platelet count 318,000/ μ L. Blood urea nitrogen was 29.4 mg/dL, creatinine 0.71 mg/dL, uric acid 7.8 mg/dL, calcium 10.5 mg/dL, phosphorus 9.2 mg/dL, sodium 141 mmol/L, potassium 5.5 mmol/L, chloride 129 mmol/L, TP 6.9 mg/dL, albumin 4.3 mg/dL, serum glucose 117 mg/dL. The venous pH was 6.82, pCO_2 20.5 mmHg, bicarbonate 3.2 mmol/L, anion gap 8.8 mmol/L. Urinalysis revealed pH 5.0, protein 3+, glucose $\pm$, blood 3+, leukocyte esterase 1+, and negative nitrite. Urine β_2 microglobulin was 9560 mg/L. Urine osmolality was 574 mOsm/kg, sodium 16 mmol/L, potassium 37.6 mmol/L, and chloride 27 mmol/L. The urine anion gap was 26.6 mmol/L, FE_{Na} was 0.01%, tubular reabsorption of phosphate 71%, urine P/Cr 3.7, FE_{UA} 17%, and urine uric acid/Cr 1.9. Intravenous saline and sodium bicarbonate infusion was started. The venous pH and bicarbonate concentration normalized on the next day. Sodium bicarbonate was tapered and discontinued on day 15. Ultrasonography revealed left grade 1 hydronephrosis. Urinalysis showed pH 7.5, negative protein, glucose, blood, 1+ leukocyte esterase, and negative nitrite. Urine culture obtained on day 14 grew *Enterococcus faecalis* 1×10^3 /mL, which was considered as asymptomatic bacteriuria. Urinalysis on day 24, however, revealed 3+ leukocyte esterase, negative nitrite, and white blood cells 50–99/HPF. Ampicillin 100 mg/kg per day was started. Urine obtained before the initiation of antibiotics grew *Enterobacter cloacae* 1×10^4 /mL. Based on the antibiotic susceptibility, ampicillin was changed to meropenem 60 mg/kg per day on day 27, which was continued until day 33. VCUG revealed pooling of contrast material in the preputial sac but no VUR. Topical corticosteroid along with the daily retraction of the foreskin resulted in the resolution of phimosis. DMSA scintigraphy performed after 6 months showed renal scarring on the upper pole of the right kidney.

Discussion

We described two preterm infants with FS associated with hydronephrosis and UTI. Patient 1 developed acute tubular necrosis after the surgery. He subsequently had UTI, and found to have bilateral VUR. FS developed after the episode of UTI, which resolved with the correction of VUR. Patient 2 had prerenal acute kidney injury associated with FS. He had complete phimosis and left mild hydronephrosis associated with bacteriuria that led to UTI.

Only one patient has previously been described who showed FS associated with obstructive uropathy [4]. This patient, a 5-day-old boy, had serum creatinine of 3.1 mg/dL and bilateral VUR associated with bilateral small kidneys. It is unknown whether the FS was due to VUR or kidney anomaly. Of interest, this patient had also distal RTA similar to Patient 1 who had bilateral small kidneys. In Patient 1, however, FS resolved after the repair of VUR, suggesting that the cause of FS is not the renal anomaly per se.

Several factors are considered as the causes of FS in our patients. The first is tubular cell stretch due to VUR in Patient 1 and obstruction due to phimosis in Patient 2. In experimental models, the expression of $\text{Na}^+\text{-K}^+\text{-ATPase}$ in tubules is decreased in obstructed kidneys [5]. Reduced expression of $\text{Na}^+\text{-K}^+\text{-ATPase}$ can lead to FS. Type IV renal tubular acidosis in association with obstructive uropathy is well known, but FS has not been reported except for the patient described above [4].

The second is infection. It is known that inflammation downregulates $\text{Na}^+\text{-K}^+\text{-ATPase}$ [6]. Again, type IV renal tubular acidosis has been reported in infants with UTI with or without obstructive uropathy [3]. The mechanism may be aldosterone inhibition by TGF- β 1 produced by inflammation [3]. TGF- β 1 as well as lipopolysaccharide, TNF- α , IL-1 β , or IFN- γ has been shown to reduce $\text{Na}^+\text{-K}^+\text{-ATPase}$ in proximal tubules [6, 7].

The third is immaturity. Both of our patients were preterm. $\text{Na}^+\text{-K}^+\text{-ATPase}$ activity rapidly increases during fetal period and after birth in animals [8, 9]. In humans also, urinary sodium excretion is high in preterm neonates, which is thought to be due to decreased $\text{Na}^+\text{-K}^+\text{-ATPase}$.

In Patient 2, severe dehydration probably caused ischemia, which probably contributed to the pathogenesis of FS. In experimental models, ischemia–reperfusion results in the downregulation of $\text{Na}^+\text{-K}^+\text{-ATPase}$ in tubules [10, 11]. Additionally, amikacin used in Patient 1 may have contributed to the pathogenesis. Aminoglycosides are endocytosed and accumulated in proximal cells causing FS [12].

In summary, we reported two preterm infants with FS associated with hydronephrosis and UTI. Immaturity, tubular cell stretch, and infection are thought to be important in the pathogenesis of FS.

Compliance with ethical standards

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Ethical standards This article does not contain any studies with animals performed by any authors.

Informed consent Informed consent was obtained from all individuals included in the study.

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