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Transient generalized proximal tubular dysfunction in an infant with a urinary tract infection: the effect of maternal infliximab therapy?

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Abstract

Objectives: Urinary tract infections (UTIs) are common in childhood. Distal tubular dysfunction during a UTI is relatively common, but proximal tubular involvement is a unique feature in humans.

Case presentation: We present the first case of transient generalized proximal tubular dysfunction (renal Fanconi syndrome) in an infant with an UTI. During pregnancy, his mother was treated for Crohn's disease with infliximab (last dose at 28 weeks of gestation). He presented at the age of six weeks with a reduced intake, and was found to have amino-aciduria, glucosuria, and urinary loss of potassium, bicarbonate and low-molecular-weight proteins. Within a few weeks after antibiotic treatment for the UTI, no proximal tubular disorder remained and the boy is doing well.

Conclusions: We hypothesize that the inflammatory response caused by the UTI was more profoundly present due to the maternal infliximab therapy, and thereby included not only the distal but also the proximal tubules.

Introduction

Urinary tract infections (UTI) are quite common in childhood, with up to 2% of boys and 7% in girls under 6 years of age suffering from at least one UTI [1]. During an acute pyelonephritis, electrolyte disturbances may present, mainly as transient hyperkalemia and pseudohypoaldosteronism in approximately one in eight children [2]. The hyperkalemia is due to inadequate potassium handling in the distal tubule, which is hypothesized to be due to aldosterone resistance that may be subsequent to tubular inflammation. Occasionally, isolated proximal tubular dysfunctions have been described during UTI, such as glucosuria [3], hypokalemia [4], and low-molecular weight proteinuria [5].

However, we present the first case of transient generalized proximal tubular dysfunction in an infant with a UTI.

Case presentation

Our patient was born at 39 weeks-of-gestation, with a birth weight of 4,000 g. The pregnancy was uneventful, except for maternal Crohn's disease that was treated with budesonide and infliximab (last dose at 28 weeks of gestation).

He presented to the general practitioner at the age of six weeks due to a reduced intake and vomiting with oral mycosis for a few days. Prior to that, he had been drinking well (up to 220 mL/kg per day of formula milk). Three days before presentation, his weight had been 4,460 g at a healthy child check-up. No fever had been noted, urine output was unchanged but the frequency of his stools was reduced.

He was admitted to a local hospital, where he was found to be irritable, had a somewhat distended abdomen without any disturbing signs, showed a varying degree of polyuria (up to 10 mL/kg/h), and to have lost weight (bodyweight 4,130 g).

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Table 1: Serum and urine parameters at presentation and follow-up.

		At presentation (six weeks of age)	At follow-up (three months of age)
Serum			
Sodium	mmol/L	131	136
Potassium	mmol/L	2.8	4.9
Calcium-ion	mmol/L	1.26	1.33
Phosphate	mmol/L	1.70	1.61
Magnesium	mmol/L	0.63	0.84
Creatinine	μmol/L	53	22
Urea	mmol/L	11.6	6.0
Glucose	mmol/L	5.2	ND
C-reactive protein	mg/L	105	ND
pH		7.25	7.38
Bicarbonate	mmol/L	16	25.3
Base excess	mmol/L	−10.4	0.0
Urine			
Albuminuria		1+	Negative
Glucosuria	mmol/L	17	ND
Sodium	mmol/L	22	ND
Potassium	mmol/L	14	ND

ND, not determined.

Laboratory work up of blood and urine at admission showed several abnormalities (Table 1), indicating generalized proximal tubular dysfunction and a potential UTI (leukocytes >50 per high power field). Also, an increased serum creatinine was noted, which normalized quickly with adequate fluids. Based on these results, antibiotics were administered after obtaining urine for culture, which later showed *E. coli*. In addition, an oral antimycotic, extra fluids, potassium and bicarbonate were administered and he was transferred to our university medical center.

Further testing confirmed the need for potassium and bicarbonate supplementation, and showed increased urinary excretion of alfa-1-microglobulin and generalized amino-aciduria (results not shown). With these results, diagnosis of renal Fanconi syndrome was made, and extensive testing was performed to elucidate the causative disease, such as cystinosis, Lowe disease, Dent disease, the Fanconi-Brickel syndrome, galactosemia, tyrosinemia, and Wilson disease (data not shown).

After rehydration, metabolic stabilisation and adequate treatment of his UTI, he was discharged home with various electrolyte (K 1.9 mmol/kg/d, Citrate 0.8 mmol/kg/d, HCO₃ 0.8 mmol/kg/d) and fluid supplementations. During follow-up, all supplements were gradually decreased and eventually stopped, while blood results remained normal and urinary losses disappeared. At the latest outpatient visit at

the age of three months, he was doing and growing well with normal lab results without supplementation (Table 1). He was found to have left-sided vesico-ureteral reflux grade II on a micturating cysto-urethrogram, for which antibiotic prophylaxis was continued.

Discussion

We describe the first case of transient renal Fanconi syndrome in a human with a UTI. Generalized proximal tubular dysfunction, or the renal Fanconi syndrome, is characterized by amino-aciduria, glucosuria, and urinary loss of substances that are handled by the proximal tubule, such as potassium, phosphate, bicarbonate and low-molecular-weight proteins [6]. With the exception of phosphate, our patient fulfilled all these criteria. Even though most cases of renal Fanconi syndrome at this young age are caused by cystinosis, an extensive evaluation was conducted to rule out other diseases. However, no abnormalities were detected during initial screening. Due to the transient nature of the tubular dysfunction, no further testing was performed.

Transient renal Fanconi syndrome has been scarcely described and was found in heavy metal poisoning [7] and drug toxicity. Only one case of UTI associated transient renal Fanconi syndrome was identified from the literature, occurring in a Labrador retriever with a chronic pyelonephritis [8]. In a later report of the same transient phenotype in a Labrador retriever, no cause was identified [9], which may suggest that these dogs may be more sensitive to develop proximal tubular dysfunction. We were unable to identify any similar cases in humans, which makes our case report unique. A study of various proteins in urine revealed that 44% of children with pyelonephritis show a mixed glomerular-tubular dysfunction, but none with isolated proximal tubular dysfunction [10], which has been described in another cohort of children with an UTI [5].

Tubular dysfunction during a pyelonephritis is relatively common, but generally limited to the distal tubule. Some proximal tubular involvement has been described, may have been the result of a more profound inflammatory response in the kidney evoked by the pyelonephritis. We hypothesize that this increased inflammatory response is due to infliximab treatment during pregnancy with subsequent effects on the immune system of the neonate. Indeed, infliximab has been shown in the offspring up to six months after delivery [11]. As our patient was only six-weeks-old when he presented with signs of Fanconi

syndrome, it is highly likely that infliximab would still have been present even though we did not have samples to prove as such. The prolonged exposure to infliximab in the neonate is based on higher levels in cord blood than in the mother in combination with the reduced clearance in the newborn [11]. Therefore, infliximab therapy in a pregnant woman may be expected to have an impact on physiological immune responses in the young child. TNF was recently shown to play a critical regulatory role in the immunological response against bacterial infections such as in the uroepithelium [12]. By blocking the innate immunity, we hypothesize that the inflammatory response caused by the UTI was more profoundly present due to the maternal infliximab therapy. The subsequently less contained, i.e. more wide-spread, infection thereby included not only the distal but also the proximal tubules. Indeed, serious infections do occur more often in patients treated with infliximab [13]. Of interest, UTIs are diagnosed more frequently in patients that are treated with TNF- α -blockers [14].

Another explanation for the transient tubular dysfunction in our patient may be found in a direct toxic effect of infliximab on the renal tubules. However, such sequelae have not been described before [11]. Based on the adequate growth, the tubular dysfunction was not present in the first few weeks of life, even though no blood or urine tests were available to test for this. Furthermore, the tubular dysfunction subsided spontaneously a few weeks later. We therefore feel that it is highly unlikely that a direct toxic effect in the proximal tubule may have played a role in the transient renal Fanconi syndrome of our patient.

In conclusion, we present the first case of generalized proximal tubular dysfunction in an infant with a UTI. We hypothesize that maternal infliximab therapy during pregnancy may have played a role in the renal reaction to the UTI that led to the proximal tubular dysfunction.

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