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An Infant Case of Transient Distal Renal Tubular Acidosis and Fanconi Syndrome Caused by Rotavirus Gastroenteritis

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We report an infant case of transient distal renal tubular acidosis and Fanconi syndrome caused by rotavirus gastroenteritis. A 10-month-old boy was admitted to the hospital because of frequent vomiting, lack of vitality, and dehydration. He was diagnosed with rotavirus gastroenteritis on account of his positive stool rotavirus antigen test. Although he presented with acidemia and severe mixed metabolic acidosis, he also had a urine pH of 6.0, indicating impaired urinary acidification. Therefore, he was diagnosed with distal renal tubular acidosis. On the third day of hospitalization, a relatively low %tubular reabsorption of phosphate level with hypophosphatemia, increased fractional excretion of uric acid with hypouricemia, and high urinary β2-microglobulin levels were observed. Moreover, he was diagnosed with Fanconi syndrome on account of multiple proximal tubular dysfunctions. After remission of rotavirus gastroenteritis, the signs of renal tubular dysfunction improved. This was a case of rotavirus gastroenteritis-caused transient distal renal tubular acidosis and Fanconi syndrome. Severe metabolic acidosis resulted from anion-gap metabolic acidosis due to acute kidney injury by rotavirus gastroenteritis and normal anion-gap acidosis due to renal tubular acidosis. When renal tubular acidosis is associated with a disease that causes anion-gap metabolic acidosis, mixed metabolic acidosis occurs and becomes exacerbated. Furthermore, it is important to consider the complications of renal tubular acidosis in the case of severe metabolic acidosis.

Keywords: distal renal tubular acidosis; Fanconi syndrome; proximal renal tubular acidosis; rotavirus; type 3 renal tubular acidosis
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Introduction

Rotavirus is one of the major pathogens of acute gastroenteritis in infants. Rotavirus gastroenteritis presents with various renal complications, such as pre-renal acute kidney injury due to dehydration and post-renal renal failure due to urinary calculi (Fujinaga et al. 2005). Moreover, increased low-molecular-weight proteinuria is observed (Yokoyama et al. 2010; Morita and Fujieda 2011), suggesting that proximal renal tubular injury may occur.

Renal tubular acidosis is a condition that results in normal anion-gap (AG) metabolic acidosis due to renal tubular dysfunction (Alexander and Bitzan 2019). It is classified mainly into distal renal tubular acidosis due to impaired hydrogen ion excretion, which causes impaired urinary acidification, and proximal renal tubular acidosis due to an impaired reabsorption of bicarbonate ions. Hereditary diseases, autoimmune diseases, and drugs cause renal tubular acidosis (Alexander and Bitzan 2019). Proximal renal tubular acidosis is often diagnosed as a symptom of Fanconi syndrome, in which the proximal renal tubular reabsorption of various substances in addition to bicarbonate ions is impaired.

We report an infant case of transient distal renal tubular acidosis and Fanconi syndrome in the case of rotavirus gastroenteritis, showing severe metabolic acidosis due to both AG and normal AG metabolic acidosis. When severe metabolic acidosis is observed, it is necessary to consider the complications of renal tubular acidosis.

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Case Presentation

A 10-month-old boy was admitted to the hospital on account of frequent vomiting, one loose stool, and dehydration (the first day of hospitalization). His body weight was 6,125 g [7,000 g before symptom onset, −2.3 standard deviation (SD) of sex- and age-matched growth curves for Japanese boys], body temperature was 37.7°C, heart rate was 140/min, and respiratory rate was 30/min. He was born by normal delivery at 36 weeks and 4 days of gestation. His birth weight was 1,964 g (−2.2 SD). Since then, his height and weight developed along the −2.0 SD of the standard growth curve. Poor weight gain was noted 3 months before admission. His mother had 9 pregnancies and 4 births. Renal disease, electrolyte abnormality, and consanguineous marriage history were not observed.

The laboratory findings upon admission (Table 1) revealed severe metabolic acidosis; high blood urea nitrogen; high uric acid; high creatinine; urine pH 6, and urine Na < Cl. Moreover, the stool rotavirus antigen test result was positive.

He was diagnosed with rotavirus gastroenteritis, as well as acute kidney injury due to dehydration, since weight loss and an increase in the blood urea nitrogen, uric acid, and creatinine levels were observed. Metabolic acidosis was accompanied by a slight increase in the AG, but ΔAG − ΔHCO_3^- was −15 mEq/L, suggesting mixed metabolic acidosis in which both AG and normal AG metabolic acidosis existed (Tsapenko 2013). Despite acidemia and metabolic acidosis, the urine pH was 6.0, suggesting impaired urinary acidification. Therefore, distal renal tubular acidosis was diagnosed (Alexander and Bitzan 2019). Fluid replacement therapy was performed. Diarrhea became more frequent after admission. On the third day of hospitalization, he ate and drank enough, and regained his vitality. Although normal AG metabolic acidosis remained, urine pH was 5.0, suggesting that the impaired urinary acidification had resolved. Conversely, urinary β2-microglobulin (β2-MG) was markedly elevated to 33,400 μg/L, %tubular reabsorption of phosphate (TRP) decreased with hypophosphatemia, and the fractional excretion of uric acid (FEUA) increased with hypouricemia. Fanconi syndrome was diagnosed on account of multiple proximal tubular dysfunctions (Alexander and Bitzan 2019). The patient's metabolic acidosis and his clinical symptoms improved, so he was discharged from the hospital on the fifth hospital day. On the 28th hospital day, the patient's body weight was 7,110 g, which was the pre-onset weight. The laboratory findings indicated mild normal AG metabolic acidosis, normalized urinary β2-MG, remission of hypophosphatemia, and hypouricemia (Table 2). Furthermore, the abdominal computed tomography image on the same day showed no calcification in the kidneys (Fig. 1).

Discussion

This case was diagnosed with transient distal renal

Table 1. Laboratory findings upon admission.

Peripheral blood		Reference range	Venous blood gases		Reference range
Red blood cells	5,560,000 /μL	3,700,000-5,700,000	pH	7.189	7.33-7.41
Hemoglobin	14.5 g/dL	10.5-14.1	pCO_2	18.9 mmHg	40.0-50.0
Platelets	345,000 /μL	150,000-400,000	HCO_3^-	6.9 mEq/L	23-27
White blood cells	15,160 /μL	6,000-17,500	Base excess	−21 mEq/L	−5.0-5.0
			Anion gap	14.1 mEq/L	9.0-13.0
Blood chemistry			ΔAnion gap-ΔHCO_3^-	−15 mEq/L	
Total bilirubin	0.15 mg/dL	0.3-2.3			
Glutamic-oxaloacetic transaminase	45 U/L	23-57	Urinalysis		
Glutamic-pyruvic transaminase	34 U/L	9-38	pH	6	
Lactate dehydrogenase	489 U/L	246-526	Protein	1+	
Creatine kinase	154 U/L	60-270	Glucose	-	
Blood urea nitrogen	29.7 mg/dL	2.9-16.7	Ketone body	1+	
Creatinine	0.33 mg/dL	0.14-0.34	Sodium	< 20 mEq/L	
Uric acid	7.6 mg/dL	2.7-6.5	Potassium	13.5 mEq/L	
Total protein	7.9 g/dL	4.9-7.4	Chloride	50 mEq/L	
Albumin	5.1 g/dL	3.1-4.8			
Sodium	144 mEq/L	135-145			
Potassium	4.6 mEq/L	4.0-5.5	Stool		
Chloride	123 mEq/L	98-108	rotavirus antigen	+	
Glucose	163 mg/dL	70-109			
C-reactive protein	0.04 mg/dL	0.06-0.3			

HCO_3^-, bicarbonate ion.

Table 2. Evaluation of renal tubular functions.

Hospital day	1	3	4	28	Reference range
Blood pH of vein	7.189	7.299	7.417	7.303	7.33-7.41
HCO_3^- (mEq/l)	6.9	18.2	27.2	19.6	23-27
AG (mEq/l)	14.1	9.8	9.2	11.4	9.0-13.0
ΔAG-ΔHCO_3^- (mEq/L)	−15	−8	0.4	−5	
Urinary pH	6.0	5.0	-	5.0	
IP (mg/dl)	-	4.0	4.5	6.0	4.8-6.7
%TRP	-	80	-	80	60-90
UA (mg/dl)	7.6	2.4	2.5	5.6	2.7-6.5
FEUA (%)	-	17.5	-	10.0	4-13
Urinary β2-MG (μg/L)	-	33,400	-	42.0	< 250

AG, anion gap; β2-MG, β2-microglobulin; FEUA, fractional excretion of uric acid; HCO_3^-, bicarbonate ion; IP, inorganic phosphorus; TRP, tubular reabsorption of phosphate; UA, uric acid.

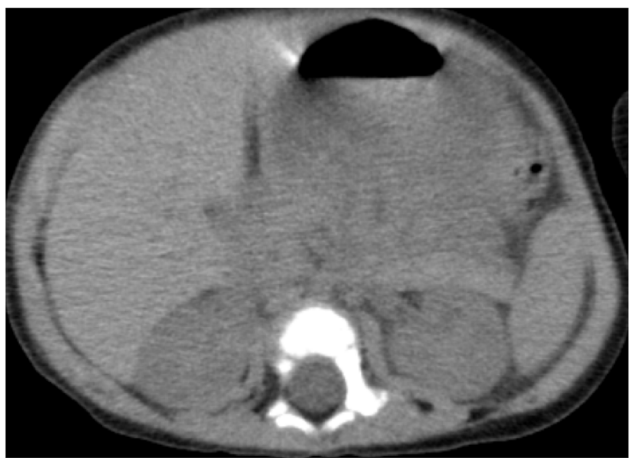

Fig. 1. An abdominal computed tomography image. Calcification in the kidneys were not observed.

tubular acidosis and Fanconi syndrome caused by rotavirus gastroenteritis. The blood gas analysis upon admission indicated a pH of 7.189 and bicarbonate ion of 6.9 mEq/L, suggesting the presence of severe metabolic acidosis. Since ΔAG − ΔHCO_3^- was −15.0 mEq/L, it was considered a mixed metabolic acidosis in which AG and normal AG metabolic acidosis co-existed (Tsapenko 2013). Distal renal tubular acidosis was diagnosed because both normal AG metabolic acidosis and impaired urinary acidification were observed at the same time. On the third day of hospitalization, a relatively low %TRP value with hypophosphatemia, increased FEUA with hypouricemia, and high urinary β2-MG level were observed. Fanconi syndrome was also diagnosed on account of multiple proximal renal tubular dysfunctions. As the uric acid level increased, FEUA decreased over time, therefore primary renal hypouricemia was less likely to exist. Normal AG metabolic acidosis improved without the administration of alkalizing drugs, which suggested that normal AG metabolic acidosis was transient. Renal calcification, which is observed in distal renal tubular acidosis, was not observed. After rotavirus gastroenteritis improved, although mild normal AG metabolic acidosis was suspected, it seemed to be within physiological variation range, since no impaired urinary acidification and proximal renal tubular dysfunctions were observed. Therefore, distal tubular acidosis and Fanconi syndrome were considered transient. Fanconi syndrome was not considered secondary to distal renal tubular acidosis, as distal renal tubular acidosis was transient (Igarashi et al. 1990; Watanabe 2005). Based on these findings, this case was diagnosed with transient distal renal tubular acidosis and Fanconi syndrome caused by rotavirus gastroenteritis. Therefore, distal renal tubular acidosis and Fanconi syndrome were not associated with the poor weight gain observed before admission.

Proximal renal tubular acidosis is a condition that causes an impaired reabsorption of bicarbonate ions in the proximal renal tubules and is often recognized as a symptom of Fanconi syndrome (Alexander and Bitzan 2019). It is caused by genetic disorders, autoimmune diseases, and drugs (Alexander and Bitzan 2019). In this case, despite no direct evidence, it can be suggested that bicarbonate ion reabsorption was impaired since multiple proximal renal tubular dysfunctions were observed. In fact, the urinary AG, which is normally positive in distal renal tubular acidosis, was negative upon admission. Diarrhea, which normally causes a positive urinary AG, was mild on admission. These implied that the negative urinary AG upon admission was due to the impaired reabsorption of bicarbonate ions, resulting in the excretion of bicarbonate ions in the urine (Berend et al. 2014; Alexander and Bitzan 2019). Essentially, bicarbonate load test is necessary to diagnose the impaired reabsorption of bicarbonate ions, but in this case, the bicarbonate load test was not possible because Fanconi syndrome and normal AG metabolic acidosis were transient. This case could be diagnosed as proximal renal tubular acidosis and also type 3 renal tubular acidosis. Type 3 renal tubular acidosis is a condition that causes both distal renal tubular acidosis and proximal renal tubular acidosis at the same time, which are thought to be rare (Alexander and

Bitzan 2019). However, a case of transient type 3 renal tubular acidosis during periodic vomiting syndrome resulting in severe metabolic acidosis has been reported (Kumagai et al. 2022). Type 3 renal tubular acidosis may be rare because it is difficult to diagnose when it is transient, as in the present case, and is therefore not well recognized.

To our knowledge, this is the first reported case of distal renal tubular acidosis and Fanconi syndrome caused by rotavirus gastroenteritis. The mechanism by which rotavirus gastroenteritis causes distal renal tubular acidosis and Fanconi syndrome is unknown. Distal renal tubular acidosis may result from impaired urinary acidification due to low concentration of urinary sodium (Santos et al. 2015; Bockenhauer et al. 2022). However, in rotavirus gastroenteritis, viremia occurs at a high rate when fever is observed (Sugata et al. 2008), and urinary β2-MG level is elevated without an increase in serum β2-MG levels (Yokoyama et al. 2010; Morita and Fujieda 2011). Moreover, rotavirus infects cultured renal epithelial cells (Londrigan et al. 2000), and a report had suggested that rotavirus was actually detected in the urine sediments of patients with rotavirus gastroenteritis (Yokoyama et al. 2011). These findings suggest that rotavirus infection of renal tubular cells may directly cause renal tubular dysfunction. Further research is needed to investigate the mechanism of renal tubular dysfunction associated with rotavirus infection.

In the present case, severe metabolic acidosis resulted from both AG metabolic acidosis due to dehydration caused by rotavirus gastroenteritis and normal AG metabolic acidosis due to distal renal tubular acidosis. Since Fanconi syndrome was also observed, an impaired reabsorption of bicarbonate ions was considered a contributing factor, which worsened the normal AG metabolic acidosis. When renal tubular acidosis, especially type 3 renal tubular acidosis, is associated with a disease that causes AG metabolic acidosis and electrolyte abnormalities (e.g., periodic vomiting syndrome), mixed metabolic acidosis occurs and becomes exacerbated, and the electrolyte abnormalities are modified (Kumagai et al. 2022). It is important to consider the complications of renal tubular acidosis, when severe metabolic acidosis is observed.

In conclusion, we report an infant case of transient distal renal tubular acidosis and Fanconi syndrome caused by rotavirus gastroenteritis, resulting in severe metabolic acidosis. If renal tubular dysfunction is caused by a disease that induces AG metabolic acidosis, severe metabolic acidosis will occur. When severe metabolic acidosis is observed, it is necessary to carefully consider the complications of renal tubular acidosis.

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Conflict of Interest

The authors declare no conflict of interest.

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