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Transient Type 3 Renal Tubular Acidosis during Cyclic Vomiting Syndrome

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Type 3 renal tubular acidosis is a pathological condition characterized by the simultaneous occurrence of distal renal tubular acidosis, which causes urinary acidification disorders, and proximal renal tubular acidosis, which causes impaired reabsorption of bicarbonate ions. Type 3 renal tubular acidosis is considered rare. A 5-year-old boy was admitted to our hospital because of frequent vomiting, poor vitality, and fever. He was diagnosed with cyclic vomiting syndrome. Type 3 renal tubular acidosis was also diagnosed because of severe mixed metabolic acidosis with impaired urinary acidification, a low tubular phosphorus reabsorption rate with hypophosphatemia, low-molecular-weight proteinuria, pan-aminoaciduria, and glucosuria. Fluid infusion was performed. On the second day of hospitalization, the vomiting disappeared and the patient was able to eat and drink. He was discharged on the eighth day of hospitalization. The laboratory test abnormalities associated with the renal tubular acidosis gradually improved, and testing at discharge on the eighth day of admission showed no metabolic acidosis, hypophosphatemia, low-molecular-weight proteinuria, or glucosuria. These findings suggested that the type 3 renal tubular acidosis was transient. Severe metabolic acidosis was observed in this patient because of both normal anion gap metabolic acidosis due to type 3 renal tubular acidosis and anion gap metabolic acidosis due to cyclic vomiting syndrome. Although type 3 tubular acidosis is rare, the resultant metabolic acidosis worsens when combined with a disease that causes metabolic acidosis. Type 3 tubular acidosis should be ruled out when severe metabolic acidosis is present.

Keywords: anion gap metabolic acidosis; cyclic vomiting syndrome; delta gap; normal anion gap metabolic acidosis; type 3 renal tubular acidosis
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Introduction

Type 3 renal tubular acidosis is a pathological condition characterized by the simultaneous occurrence of distal renal tubular acidosis, which causes urinary acidification disorders, and proximal renal tubular acidosis, which causes impaired reabsorption of bicarbonate ions (Alexander and Bitzan 2019). Type 3 renal tubular acidosis is rare and caused by congenital type 2 carbonic anhydrase II deficiency and drugs such as topiramate (Sacré et al. 2006; Alexander and Bitzan 2019).

Cyclic vomiting is a syndrome in which sudden and frequent vomiting occurs periodically (Li 2018; Maqbool et al. 2020). At admission, more than half of patients with cyclic vomiting require fluid infusion and may show high ketone body concentrations, anion gap metabolic acidosis, and electrolyte abnormalities (Li et al. 2008). No reports of cyclic vomiting have described renal tubular acidosis as a complication.

We experienced a case of transient type 3 renal tubular acidosis during cyclic vomiting syndrome. Severe metabolic acidosis was observed in this case because of both normal anion gap metabolic acidosis due to type 3 renal tubular acidosis and anion gap metabolic acidosis due to cyclic vomiting syndrome. Although type 3 renal tubular acidosis is rare, it is important to rule out type 3 renal tubular acidosis when severe metabolic acidosis is observed.

Case Presentation

A 5-year-old boy was admitted to our hospital because of frequent vomiting, poor vitality, and fever. No diarrhea was observed. He was diagnosed with cyclic vomiting syn-

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drome. Although he had developed several episodes of cyclic vomiting syndrome, he had experienced no complications such as renal tubular acidosis. His weight was 18.8 kg [0.47 standard deviation (SD)], and his height was 109 cm (0.40 SD). He was born by normal delivery at 40 weeks and 4 days of gestation. His birth weight was 3,346 g (0.52 SD), and his birth height was 50 cm (0.15 SD). No growth failure was observed.

Laboratory examinations (Table 1) revealed marked metabolic acidosis; high creatinine, uric acid, and ketone body concentrations; and low sodium, chloride, and phosphate concentrations. Urinalysis showed urinary acidification disorder with a pH of 6.5 despite metabolic acidosis, glucosuria, urine ketones, low-molecular-weight proteinuria, pan-aminoaciduria, and a low phosphorus reabsorption rate. Urinary organic acid analysis showed a nonspecific result. Renal ultrasonography showed no renal calcification.

Because the delta gap, calculated as the rise in the anion gap minus the fall in bicarbonate ion (i.e., ΔAG−ΔHCO_3^-), was −10, the patient's acidosis was considered to be a mixed metabolic acidosis characterized by the coexistence of both anion gap metabolic acidosis and normal anion gap metabolic acidosis. Mixed metabolic acidosis with urinary acidification disorder, a low phosphorus reabsorption rate with hypophosphatemia, low-molecular-weight proteinuria, pan-aminoaciduria, and glucosuria led to the diagnosis of type 3 renal tubular acidosis as a complication. Fluid infusion was performed. The patient underwent infusion of 1,200 ml of fluid (sodium, 130 mEq/L; potassium, 4 mEq/L; chloride, 109 mEq/L; glucose, 50 g/L) over a 24-hour period. On the second day of hospitalization, the vomiting disappeared and the patient was able to eat and drink. The fever disappeared on the third day of hospitalization. He was discharged on the eighth day of hospitalization. The laboratory test abnormalities associated with the renal tubular acidosis gradually improved (Table 2), and testing at discharge on the eighth day of admission showed no metabolic acidosis, hypophosphatemia, low-molecular-weight proteinuria, or glucosuria. These finding suggested that the type 3 renal tubular acidosis was transient.

Discussion

The tubular dysfunction in this case was diagnosed as type 3 renal tubular acidosis. Type 3 renal tubular acidosis is caused by congenital carbonic anhydrase II mutation and drugs such as topiramate (Sacré et al. 2006; Alexander and Bitzan 2019). Most of the cases previously diagnosed as type 3 renal tubular acidosis were considered to be proximal renal tubular acidosis secondary to distal renal tubular acidosis (Igarashi et al. 1990; Watanabe 2005; Quigley and Wolf 2015). We diagnosed our patient's condition as distal renal tubular acidosis because of normal anion gap metabolic acidosis and urinary acidification disorder despite the presence of metabolic acidosis. Impaired reabsorption of bicarbonate ion was not directly demonstrated; however, the presence of normal anion gap metabolic acidosis, a low

Table 1. Laboratory findings on admission.

Peripheral blood		Blood chemistry		Urinanalysis	
Red blood cells	5,160,000/μL	Total bilirubin	0.5 mg/dL	pH	6.5
Hemoglobin	14.2 g/dL	Glutamic-oxaloacetic transaminase	22 U/L	Protein	2+
Hematocrit	44%	Glutamic-pyruvic transaminase	16 U/L	Occult blood	−
Platelets	369,000/μL	Lactate dehydrogenase	202 U/L	Glucose	1+
White blood cells	15,600/μL	Alkaloine phosphatese	138 U/L	Ketone body	4+
		Creatine kinase	26 U/L	Sodium	11 mEq/L
Venous blood gases		Blood urea nitroge	18.9 mg/dL	Potassium	29 mEq/L
pH	7.192	Creatinine	0.29 mg/dL	Chloride	37 mEq/L
pCO_2	14.5 mmHg	Uric acid	15.8 mg/dL	Protein/Creatinine	1.818 g/gCr
HCO_3^-	5.4 mmol/L	Total protein	7.5 g/dL	NAG	4.3 U/L
Base excess	−20 mmol/L	Albumin	4.6 g/dL	β2-MG	36,339 μg/L
Anion gap	20.6 mmol/L	Sodium	127 mEq/L	Pan aminoacduria	+
ΔAniong gap-ΔHCO_3^-	−10 mmol/L	Potassium	4.8 mEq/L	%TRP	37.1%
Lactic acid	14.4 mg/dL	Chloride	101 mEq/L		
		Calcium	11.7 mg/dL		
		IP	1.3 mg/dL		
		C-reactive protein	2.41 mg/dL		
		Glucose	94 mg/dL		
		Total ketone body	8,265 μmol/L		

HCO_3^-, bicarbonate ion; TRP, tubular reabsorption of phosphate; IP, Inorganic phosphorus; NAG, N-acetyl-β-D-glucominidase; β2-MG, β2-microglobulin.

Table 2. Evaluation of renal tubular functions.

	On admission	8 hours after admission	Day 2	Day 3	Day 4	Day 6	Day 8	Day 29
Blood chemistry								
IP (mg/dL)	1.3	1.3				4.5	4.3	4.8
Creatinine (mg/dL)	0.29	0.2				0.19	0.21	0.19
Venous blood gases								
pH	7.192	7.365					7.437	7.414
HCO_3^- (mmol/L)	5.4	11.5					26.4	21.2
Anion gap (mmol/L)	20.6	15.5						
ΔAnion gap-ΔHCO_3^-	−10.0	−9						
Urinanalysis								
pH	6.5		6.5	7.5	8.5	8	8.5	7.5
NAG (U/L)	4.3		12.4	4.4	3.1	28.2	2.4	2
β2-MG (μg/L)	36,339		9,585	275	122	365	388	136
Glucose	1+		−	2+	2+	−	−	−
Ketone body	4+		3+	−	−	nd	−	−
%TRP (90.5-92.5)	37.1						93.8	98.1
Pan aminoaciduria	+							

IP, Inorganic phosphorus; HCO_3^-, bicarbonate ion; NAG, N-acetyl-β-D-glucominidase; β2-MG, β2-microglobulin; TRP, tubular reabsorption of phosphate.

tubular phosphorus reabsorption rate with hypophosphatemia, low-molecular-weight proteinuria, pan-aminoaciduria, and glucosuria suggested Fanconi syndrome. In addition to the normal anion gap metabolic acidosis, most of the proximal tubular function was impaired, suggesting that impaired reabsorption of bicarbonate ion was highly probable. Therefore, proximal renal tubular acidosis was diagnosed. Because the distal renal tubular acidosis was transient, the proximal renal tubular acidosis was not secondary to the distal renal tubular acidosis. The patient was diagnosed with type 3 renal tubular acidosis because both distal renal tubular acidosis and proximal renal tubular acidosis existed at the same time. If proximal renal tubular acidosis is transient and complicated by distal renal tubular acidosis, the proximal renal tubular acidosis is difficult to diagnose because of difficulty performing a bicarbonate load test. Type 3 renal tubular acidosis may be rare because it is difficult to diagnose when transient, as in the present case, and is therefore not well recognized.

To the best of our knowledge, this is the first reported case of cyclic vomiting syndrome complicated by type 3 renal tubular acidosis to date. After the patient's vomiting improved, the laboratory abnormalities associated with type 3 renal tubular acidosis promptly improved, and no abnormal findings were observed during subsequent hospital visits. This outcome suggests that the type 3 renal tubular acidosis was caused by cyclic vomiting syndrome. The mechanism by which cyclic vomiting causes type 3 renal tubular acidosis is unknown. Cyclic vomiting is a syndrome in which sudden and frequent vomiting occurs periodically (Li 2018; Maqbool et al. 2020). At admission, more than half of patients with cyclic vomiting require fluid infusion and may show high ketone body concentrations, anion gap metabolic acidosis, and electrolyte abnormalities (Li et al. 2008). In the present case, severe metabolic acidosis occurred because of normal anion gap metabolic acidosis associated with type 3 renal tubular acidosis in addition to anion gap metabolic acidosis associated with cyclic vomiting syndrome. When type 3 renal tubular acidosis is associated with a disease that causes anion gap metabolic acidosis and electrolyte abnormalities (such as cyclic vomiting syndrome), mixed metabolic acidosis occurs and becomes exacerbated, and the electrolyte abnormalities are modified. Although type 3 renal tubular acidosis is rare, it is important to rule out when severe metabolic acidosis is observed.

The acid-base equilibrium at admission in this case showed a bicarbonate concentration of 5.4 mmol/L and anion gap of 20.6 mmol/L, suggesting anion gap metabolic acidosis. However, because the delta gap ($\Delta AG-\Delta HCO_3^-$) was −10, normal anion gap metabolic acidosis was also suggested. Mixed metabolic acidosis was diagnosed because both anion gap metabolic acidosis and normal anion gap metabolic acidosis coexisted (Tsapenko 2013; Berend et al. 2014). $\Delta AG-\Delta HCO_3^-$ is an index used to evaluate mixed metabolic acid-base imbalance. ΔAG is an increase from the standard anion gap, and ΔHCO_3^- is a decrease from the standard bicarbonate. $\Delta AG-\Delta HCO_3^-$ of ≥ 5 suggests that the patient's condition is complicated by metabolic alkalosis, and $\Delta AG-\Delta HCO_3^-$ of less than −5 sug-

gests that the condition is complicated by normal anion gap metabolic acidosis (Tsapenko 2013; Berend et al. 2014). In the present case, mixed metabolic acidosis was inferred from $\Delta AG-\Delta HCO_3^-$, leading to the diagnosis of type 3 renal tubular acidosis. In patients with metabolic acidosis, evaluation of $\Delta AG-\Delta HCO_3^-$ is clinically important because it can more accurately indicate the pathological condition causing metabolic acidosis.

In conclusion, transient type 3 renal tubular acidosis may be rare because it is difficult to diagnose. If type 3 renal tubular acidosis is associated with a disease that causes metabolic acidosis, the metabolic acidosis can be as severe as in the present case. In patients with metabolic acidosis, it is important to evaluate $\Delta AG-\Delta HCO_3^-$ to more accurately evaluate the pathophysiology of metabolic acidosis.

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Conflict of Interest

The authors declare no conflict of interest.

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