Oral Proton Pump Inhibitor for Treatment of Congenital Chloride Diarrhea

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ABSTRACT

Congenital chloride diarrhea (CCD) is a rare autosomal recessive disease, which is characterized by electrolyte absorption defect due to impaired function of the $\text{Cl}^-/\text{HCO}_3^-$ exchanger in the ileum and the colon. Its main features are profuse watery diarrhea, high fecal chloride concentration, and failure to thrive. Profuse watery diarrhea characterized by a high concentration of chloride in stools results in hypochloremia, hyponatremia, and dehydration with metabolic alkalosis. Early detection and therapeutic intervention can prevent life-threatening symptoms of CCD and growth failure. Recently, several therapies, such as proton pump inhibitors and butyrate, have been suggested for amelioration of diarrhea. Here, we report a case of CCD in a preterm male infant who was successfully treated with an oral proton pump inhibitor.

Key Words: Congenital chloride diarrhea, Alkalosis, *SLC26A3*, Proton pump inhibitor, Omeprazole

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INTRODUCTION

Congenital chloride diarrhea (CCD) is a rare autosomal recessive disease, which is characterized by defective absorption of chloride in the intestine. In 1945, two cases of this disease, which presented with congenital diarrhea and metabolic alkalosis, were described for the first time by Gamble and Darrow^{1,2)}. To date, more than 250 CCD cases have been reported worldwide³⁾. The incidence in Finland is approximately 1:30,000 to 1:40,000, accounting for approximately one-fifth of the reported cases³⁾. Higher incidence (>1:20,000) was reported in patients from Poland, Kuwait, and Saudi Arabia^{3,4)}. The incidence of CCD in Korea and other East Asian countries has not been evaluated thus far and only a few CCD cases have been reported⁵⁾. CCD is caused by mutations in the solute carrier family 26 member 3 gene (*SLC26A3*) located on chromosome 7q31, which encodes the transmembrane $\text{Cl}^-/\text{HCO}_3^-$ exchanger present in the apical membrane of the ileum and the colon^{3,6,7)}. A total of 55 mutations in *SLC26A3* have been identified

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worldwide thus far⁸⁾. The majority of mutation types are single nucleotide substitutions (55%), followed by small deletions/insertions or their combinations (38%), large deletions (5%), and insertions (2%)⁸⁾. These mutations result in defective absorption of Cl^- and secretion of HCO_3^- in the intestine, leading to Cl^- rich watery diarrhea^{3,6,7)}. Because of this intestinal loss of ions and fluid, the patient experiences hypochloremia, hyponatremia, and dehydration. These conditions activate the renin-angiotensin system, which causes both hypokalemia and metabolic alkalosis³⁾. Accurate diagnosis and correction of electrolyte imbalance will restore normal growth and development with favorable prognosis. Recently, several drugs such as proton pump inhibitors and butyrate have been suggested as effective and successful therapies for diarrhea^{3,9,10)}. Here, we report a case of CCD in a preterm male infant with a mutation in the *SLC26A3* gene who was successfully treated by oral administration of the proton pump inhibitor omeprazole.

CASE REPORT

A 30-year-old woman with a history of one pregnancy and one abortion was referred to our hospital at an estimated gestational age of 32 weeks with abdominal pain and polyhydramnios. Previous fetal ultrasonography revealed polyhydramnios and a dilated fetal bowel loop. Hence, the newborn was suspected to have congenital small bowel obstruction or atresia (Figure 1). Since fetal ultrasonography at estimated 34-week gestational age showed severe progression of polyhydramnios and persistence of the dilated small bowel condition in

Figure 1. Prenatal ultrasonography of a male fetus (estimated gestational age: 34⁺¹ weeks) showing dilatation of bowel loops.

the fetus, a male newborn was delivered by a cesarean section at estimated 34⁺⁷ week gestational age with a birth weight of 2,800 g. The Apgar score was 8 and 9 at 1 and 5 minutes after birth, respectively. Physical examination revealed a soft and distended abdomen with normal bowel sounds. The newborn did not exhibit hepatomegaly, splenomegaly, or palpable mass. Other physical examinations reported normal results and newborn's vital signs were stable after birth. Abdominal X-ray demonstrated dilatation of bowel loops. However, there was no evidence of small or large bowel obstruction as shown by abdominal ultrasonography and water-soluble contrast study of the gastrointestinal tract. After the abdominal distension was reduced by inserting an orogastric tube for 3 days, the newborn received enteral nutrition. He was discharged at 9 days of age.

One week later, the newborn infant was admitted to hospital for icteric skin color and lethargic condition at 17 days of age. Urine-like watery diarrhea about 10 times per day with insufficient sucking was also observed. In laboratory tests, hyponatremia (serum sodium, 124 mmol/L), hypochloremia (serum chloride, 75 mmol/L), and metabolic alkalosis (blood pH, 7.69 and base excess, 14.2 mmol/L) were identified. Abdominal X-ray showed a severe distension of bowel loops when compared to the condition seen during initial observations (Figure 2). Since CCD could be caused by single gene mutation, genetic testing was performed to confirm the diagnosis. After obtaining an informed consent from patient's parents, peripheral blood

Figure 2. Plain abdominal radiographs of the same patient during the second admission showed marked dilatation of bowel loops with air.

was collected from the patient and his parents for deoxyribonucleic acid (DNA) extraction. Sequence analysis of the *SLC26A3* gene identified a homozygous transition (G to T) in the splice acceptor site of intron 18 (c.2063-1G>T). In the familial study, patient's father and mother were found to be heterozygous carriers of c.2063-1G>T (Figure 3). After confirming the diagnosis of CCD, oral omeprazole 2 mg/kg/day was added to fluid concomitantly with sodium supplementation at one month of age. Two days after the start of omeprazole treatment, the frequency of stool passages decreased from 10 to 4 times per day. Intravenous fluid therapy for electrolyte correction was discontinued and oral treatment with 3 mEq/kg/day sodium chloride (NaCl) was initiated. At the time of discharge, the patient was able to take all formula feeds by mouth and serum electrolytes were stable after oral NaCl administrations. After discharge, his serum electrolytes were within the normal range even though the amount of oral NaCl was reduced subsequently. At the same time, omeprazole treatment was continued and adjusted for his increased weight.

At 9 months of age, the patient continued to receive 2 mg/kg/day omeprazole and electrolyte supplementation with 1 mEq/kg/day NaCl. His weight and height were 9.1 kg (50th percentile) and 74.7 cm (25th percentile), respectively. He had normal growth and development without obvious electrolyte imbalance. We planned to make the transition to usual solid food without an additional salt replacement.

DISCUSSION

Clinical characteristics of CCD include watery diarrhea in the intrauterine phase. Prenatal signs of CCD, such as polyhy-

dramnios and a dilated bowel loop of the fetus, are visible on prenatal ultrasonography even in the end of the second trimester³. Other complications include preterm birth, severe polyhydramnios requiring therapeutic amniocentesis, and unnecessary surgery in neonates³. It is necessary to rule out intestinal obstruction, such as small bowel atresia or congenital megacolon, particularly when newborns present with delayed passage of meconium and distended abdomen^{3,11}.

The infant may have profuse watery diarrhea, which can be mistaken for urine, for several days. Due to this persistent watery diarrhea, dehydration and excessive weight loss will develop in patients with CCD. Metabolic alkalosis and electrolyte imbalance will be usually revealed in laboratory investigations. If left untreated, these conditions can be fatal, as metabolic alkalosis and electrolyte imbalance can lead to arrhythmia and severe dehydration³. Untreated conditions may also result in developmental retardation, chronic kidney disease, and male subfertility³. The clinical characteristics and long-term outcomes of CCD cases reported in Korea are summarized in Table 1¹²⁻¹⁶.

Diagnosis of CCD is based on the measurement of high fecal chloride (>90 mmol/L) and acidic pH³. High concentration of fecal chloride is still sufficient to confirm the diagnosis. Currently, genetic analysis is available for the detection of CCD-related *SLC26A3* mutations and a total of 55 mutations have been reported⁸. In Korea, genetic analysis results of 8 CCD patients have been published, and it was suggested that c.2063-1G>T mutation could have been a founder mutation in Korean population⁵. Our case also demonstrated the presence of the homozygous c.2063-1G>T mutation in our patient confirming the above notion that it could be a genuine founder mutation.

From the therapeutic point of view, salt substitution therapy is the standard CCD treatment, while the management of acute

Figure 3. DNA sequence analysis of *SLC26A3*. (A) The patient had a homozygous transition at the splice acceptor site of intron 18 (c.2063-1G>T). (B) The patient's father and (C) mother were found to be heterozygous carriers of c.2063-1G>T (black arrow).

Table 1. The clinical characteristics of the patients with congenital chloride diarrhea in Korea

Source	Sex	Gestational age (wks)	Body weight (kg)	Age of diagnosis	Symptoms	Gene mutation	Treatment	Duration of follow-up	Long-term prognosis
Seo et al. ¹²⁾ (1998)	F	36 ⁺⁴	3.5	3 months	Chronic diarrhea Lethargic condition	No description	Electrolyte replacement	2 years	Favorable
Yoon et al. ¹³⁾ (2003)	F	36 ⁺⁴	2.9	21 days	Dilated abdomen Chronic diarrhea	No description	Electrolyte replacement	5 months	Favorable
Lee et al. ¹⁴⁾ (2012)	M	34 ⁺⁵	2.8	Before 1 month	Chronic diarrhea	c.525G>C c.2063-1G>T	Electrolyte replacement	3 months	Favorable
Yim et al. ¹⁵⁾ (2012)	M	33	2.9	1 day	Dilated abdomen Chronic diarrhea	No description	Electrolyte replacement	40 days	No description
Seo et al. ¹⁶⁾ (2013)*	M	32 ⁺²	2.1	6 month	Failure to thrive Developmental delay	No description	Electrolyte replacement	19 months	Unfavorable
	F	32 ⁺²	1.7	6 month	Chronic diarrhea Growth retardation	No description	Electrolyte replacement	19 months	Favorable
The present study	M	34 ⁺⁵	2.8	1 month	Icteric skin color Lethargic condition	c.2063-1G>T c.2063-1G>T	Electrolyte replacement Omeprazole	9 months	Favorable

* These two cases were twins.

dehydration and electrolyte imbalance during acute gastroenteritis or other infections is also necessary³⁾. The combination therapy with both NaCl and potassium chloride (KCl) via the oral or intravenous route will protect against common CCD complications. The optimal dosage of chloride ranges from 6 to 8 mmol/kg/day in infants and from 3 to 4.4 mmol/kg/day in older children^{3,17)}.

Several therapies for diarrhea have been recently suggested in several cases. Omeprazole, a proton pump inhibitor, has been found to reduce watery diarrhea¹⁰⁾. Omeprazole decreases intestinal chloride loss by protecting endogenous chloride stores and by reducing the amount of chloride presented in the intestinal tract¹⁰⁾. Butyrate, a short-chain fatty acid, was also used to alleviate watery diarrhea through the activation of a parallel Cl⁻/butyrate and Na⁺/H⁺ exchanger¹⁸⁾. In addition, cholestyramine decreased watery diarrhea symptoms to a certain extent, but its therapeutic action was moderate and transient³⁾.

There have been several reported cases of CCD that were successfully treated with omeprazole. Fuwa et al.¹⁹⁾ used omeprazole and butyrate for reducing watery diarrhea and their patient displayed normal growth without electrolyte supplementation. Pieroni et al.⁹⁾ described a CCD patient who received long-term omeprazole, which maintained serum electrolyte balance without NaCl and KCl supplementation. In our case, we also found that omeprazole strongly reduced watery diarrhea symptoms and corrected electrolyte imbalance. However, close

monitoring of the efficacy of and adverse reactions associated with omeprazole is necessary because its utility and safety as an anti-diarrheal have not been sufficiently verified in CCD patients thus far. Because no official guidelines for omeprazole use in CCD patients have been published to date, we are planning manage diarrhea with omeprazole maintenance therapy and carefully monitor electrolyte imbalance and symptom severity. In conclusion, we have reported a case of CCD with a SLC26A3 mutation, which was successfully treated with omeprazole according to suggestions in the literature.

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