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Case Report / Olgu Sunumu

SLC26A3 mutation in Turkish neonate and her sibling with congenital chloride diarrhea

Türk yenidoğan ve konjenital klorür diyareli kardeşinde SLC26A3 mutasyonu

Erkan Doğan[1], Eylem Sevinç[2], Mehmet Akif Göktaş[3], Sadrettin Ekmen[1], Nihal Yıldız[1]

[1]Department of Child Health and Diseases, Karabük University Faculty of Medicine, Karabük, Turkey
[2]Division of Pediatric Gastroenterology, Department of Child Health and Diseases, Karabük University Faculty of Medicine, Karabük, Turkey
[3]Division of Pediatric Gastroenterology, Department of Child Health and Diseases, Erciyes University Faculty of Medicine, Kayseri, Turkey

The known about this topic

Congenital chloride diarrhea is characterized by life-long watery diarrhoea of prenatal onset with high faecal Cl- concentration. The diagnosis of congenital chloride diarrhea is often delayed. No siblings with congenital chloride diarrhea have been reported previously in Turkey.

Contribution of the study

The first siblings case with congenital chloride diarrhea reported from Turkey.

Abstract

Congenital chloride diarrhea is a rare cause of severe infantile diarrhea with excessive chloride excretion. Mutations in the SLC26A3 gene cause congenital chloride diarrhea. It generally becomes apparent in the neonatal period and is characterized by electrolyte imbalances, metabolic alkalosis, and failure to thrive. The diagnosis of congenital chloride diarrhea is based on detecting excessive chloride in the stool (90 mmol/L). We report a Turkish neonate with congenital chloride diarrhea whose sibling had the same disease. The newborn was born by cesarean delivery. Diarrhea, vomiting, and weight loss started soon after birth. She was diagnosed as having congenital chloride diarrhea based on its typical clinical signs and a high concentration of stool chloride and was confirmed by genetic analysis. She was treated by means of salt supplementations and lansoprazole. Family history may play an important role in the early diagnosis because the disease is inherited autosomal recessively.

Keywords: Congenital chloride diarrhea, neonate, polyhydramnios, SCL26A3, sibling

Öz

Konjenital klor diyaresi bebeklerde artmış klor atılımının olduğu ciddi ishalin ender bir nedenidir. SLC26A3 genindeki mutasyonlar konjenital klor diyaresine neden olur. Belirtiler genellikle yenidoğan döneminde başlar ve elektrolit dengesizliği, metabolik alkaloz ve gelişme geriliği ile belirgin olur. Konjenital klor diyaresi tanısı dışkıda artmış klor (90 mmol/L) atılımının saptanmasına dayanır. Kardeşinde de aynı hastalık bulunan konjenital klor diyareli Türk yenidoğanı bildiriyoruz. Yenidoğan sezaryen yolla doğdu. Doğumdan hemen sonra ishal, kusma ve tartı kaybı başladı. Konjenital klor diyaresi tanısı tipik klinik belirti ve dışkıda artmış klor konsantrasyonuna dayanarak kondu ve genetik analizle doğrulandı. Tuz desteği ve lansaprazol ile tedavi edildi. Hastalık otozomal çekinik kalıtım gösterdiğinden, erken tanıda aile öyküsünün olması önemli bir rol oynayabilir.

Anahtar sözcükler: Kardeş, konjenital klor diyaresi, polihidroamnios, SCL26A3, yenidoğan

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Introduction

Congenital chloride diarrhea (CCD) is a rare autosomal recessive disorder that presents in newborn infants as secretory diarrhea. Its incidence is estimated as 1:10,000 to 1:40,000 births. Most children with CCD were reported from Kuwait and Saudi Arabia (1). It is caused by a defect in active transport of Cl^-/HCO_3 in the bowel, resulting in chloride-rich diarrhea with electrolyte imbalance and metabolic alkalosis. Affected newborn usually present

Corresponding Author/Sorumlu Yazar: Eylem Sevinç E-mail/E-posta: dr.eylemsevinc@gmail.com
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with watery diarrhea resulting in severe dehydration and weight loss. Accurate diagnosis and correction of biochemical abnormalities with electrolyte supplements is the cornerstone of management (2).

Case

A 32-year-old woman found to have polyhydramnios at 34 weeks of pregnancy was referred to the Division of Pediatric Gastroenterology at Karabuk Education and Training Hospital in September 2017. She had some concerns because her first child was diagnosed as having CCD. She wondered whether the fetus had CCD disease. In the family history, there was no consanguinity. Two weeks later, a female baby was born by cesarean section.

The female newborn weighed 3200 g, its length was 50 cm, with Apgar score 7 (1 min) and 9 (5 min). Watery diarrhea and vomiting started soon after birth. She required admission to the neonatal intensive care unit (NICU) because of dehydration and poor feeding with 15% weight loss. A physical examination revealed a distended abdomen. Blood gas and serum biochemical analysis were performed after birth. Blood analyses showed hypochloric hypokalemic metabolic alkalosis with pH 7.55, and base excess +3.2 sodium (Na^+) 129 mmol/L, potassıum (K^+) 3.4 mmol/L, and chloride (Cl^-) 86 mmol/L. The stool test was initially within normal limits. Both abdominal X-ray and ultrasound revealed diffuse dilated intestinal loops. The family history along with polyhydramnios, watery diarrhea, bowel distension, and metabolic alkalosis led to a suspicion of CCD. Therefore, additional laboratory studies were performed: stool and urine electrolyte, sweat Cl, and plasma renin levels. Her stool electrolytes were as follows: Na^+ of 52 (ref: 20–30) mmol/L, K^+ of 61 (ref: 55–65) mmol/L, and Cl^- of 125 (ref: 5–20) mmol/L. Cystic fibrosis was ruled out through a negative sweat test. The other laboratory results showed a low urine Cl concentration of 28 (ref: 110–250) mmol/L, high plasma renin activity and aldosterone levels, 42.6 (ref: 2.9–40) ng/mL/hour and 892.9 (ref: 29.5–162) pg/mL, respectively. The first results were similar to Bartter syndrome (BS); however, after intravenous fluid and electrolyte therapy, the plasma renin and aldosterone levels returned to normal values (Table 1). She was diagnosed as having CCD based on its typical clinical signs and a high concentration of stool Cl^-. Consent was obtained from the patient's parent.

The diagnosis was confirmed through genetic analysis. Our patient and her sister carry the same mutation c.2024_2026dup TCA (pIle675_Arg676insIle) in exon 18 of the SLC26A3 gene in a homozygous state. She was initially treated with intravenous fluids, administration of oral NaCl (3 mg/kg/day) and KCl (2 mg/kg/day) supplementation with lansoprazole (2 mg/kg/day) was changed to peroral therapy within 1 week. She tolerated oral salt supplementations with lansoprazole well. At six months of age, she still had diarrhea 5–6 times a day despite salt supplementations with lansoprazole.

Table 1. Results of laboratory tests at different follow-up periods

	Day 1	Day 3	Day 15	Day 180
Na^{+a} (mmol/L)	129	134	137	138
K^{+a} (mmol/L)	3.4	3.9	4.2	4
Cl^{-a} (mmol/L)	86	90	94	95
Plasma renin activity (ng/mL/hour)		42.6	21.3	
Aldosterone (pg/mL)		892.9	113.5	
phb	7.55	7.49	7.43	7.37
HCO_3^b	39	37	31	29
PCO_2^b	33	36	41	38
Na^{+c} (mmol/L)		52	48	32
K^{+c} (mmol/L)		61	58	54
CI^{-c} (mmol/L)		125	105	88

[a]Serum; [b]Blood gas analyses; [c]Stool

Discussion

Since the first case report of CCD published by Gamble et al. (3) in 1945, more than 250 cases of CCD have been reported in the world. At the beginning of the year 2000, the first siblings with CCD were diagnosed by Yoshikava (4). In 2013, the first dizygotic twins with CCD were reported by Seo et al. (5). To our knowledge, no siblings with CCD have been reported previously in Turkey.

Infants affected with CCD usually present with severe watery diarrhea, abdominal distention, and repeated vomiting within the first hours of life (2). Shamaly et al. (6) reported a newborn with CCD presenting with mainly ileus and abdominal distention without diarrhea in 2013. In our patient, the presentation was mainly with watery diarrhea and vomiting.

Congenital chloride diarrhea may be suspected in prenatal ultrasound scans in fetuses with polyhydramnios and bowel dilatation from the second trimester of pregnancy. Kawamura et al. (7) reported that magnetic resonance imaging (MRI) was a useful imaging tool for diagnosing fetal CCD. In our patient, fetal ultrasound showed polyhydramnios and bowel dilatation; however, MRI was not performed.

The diagnosis of CCD is based on clinical symptoms and the measurement of chloride concentration in the stool. Gils et al. (8) developed a new method to measure Cl^- in stool. They used an ordinary gas analyzer but it has not yet entered into routine use. To confirm the diagnosis, genetic analysis can be made but it is not absolutely nec-

essary (3). Our patient was easily diagnosed as having CCD because of the onset of diarrhea soon after birth, elevated stool Cl^-, hypochloremic metabolic alkalosis, antenatal polyhydramnios, and most importantly, family history.

The siblings of a patient with CCD may be at higher risk of developing this disorder because CCD is an autosomal recessive disorder. More than 55 different mutations in the SLC26A3 gene have been reported in patients with CCD (9). In our patient, a homozygous mutation was found: c.2024_2026dup TCA (pIle675_Arg676insIle) in exon 18 of the SLC26A3 gene. The patient's sister has the same mutation. The mutation was also reported in other countries.

Early neonatal persistent hypochloremic metabolic alkalosis can be caused by a number of conditions. It mainly includes cystic fibrosis (CF), pyloric stenosis, BS, and CCD. It may also be difficult to distinguish each other in neonatal period because clinical signs of these diseases often overlap (4). We excluded CF with a negative sweat test. Bartter syndrome is characterized by hypochloremic metabolic alkalosis and increased urinary chloride excretion. In our patients, urinary chloride excretion was low.

The primary treatment for CCD is life-long salt substitution, which prevents the development of hypochloremic metabolic alkalosis and increases intestinal absorption. Other drugs for CCD include proton pump inhibitor, butyrate, and cholestyramine. It has been demonstrated that these drugs significantly reduce the volume and frequency of stools (2). Bin Islam et al. (10) reported that captopril significantly reduced the volume of stools and might be effective in the treatment of CCD. Our patient was given oral NaCl and KCl with lansoprazole therapy. She is under control and has normal growth and development.

In conclusion, CCD is a rare inherited condition in early infancy and should be identified as early as possible. Family history may play a critical role in the diagnosis of CCD because the disease is inherited autosomal recessively. This is the first case report of siblings with the same homozygous mutation in SCL26A3 from Turkey.

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