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

Turk yenidoğan ve konjenital klorür diyareli kardeșinde SLC26A3 mutasyonu

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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 supplements 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 artışa klor atımının olduğu ciddi ishâlın 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 disseminationa armtş klor (90 mmol/L) atımının saptanmasına dayanır. Kardeşinde de aynı hastalık beliri bulunun konjenital klor diyareli Türk yenidoğanı bildiriyoruz. Yenidoğan seşareen yolğa doğdu. Doğumdan hemen sonra ishal, kusma ve tartı kaybı başladı. Konjenital klor diyaresi tanısı tipik klinik belirti ve dışkı-dan artış klor konsantrasyonuna dayanarak konu ve genetik analizle doğrulandı. Tuz desteği ve lansoprazol ile tedavi edildi. Hastalık otozomal çekinik kalıtın gösterdiğiinden, erken tanda aile öyküsünün olması önemli bir rol oynamabilir.

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

Cite this article as: Doğan E, Sevinç E, Göktâş MA, Ekmen S, Yıldız N. SLC26A3 mutation in Turkish neonate and her sibling with congenital chloride diarrhea. Turk Pediatri Ars 2020; 55(1): 76–8.

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⁻/HCO₃⁻ in the bowel, resulting in chloride-rich diarrhea with electrolyte imbalance and metabolic alkalosis. Affected newborn usually present...
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, potassium (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 distention, 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 (p.Ile675_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⁺ (mmol/L) | 129 | 134 | 137 | 138 |
| K⁺ (mmol/L) | 3.4 | 3.9 | 4.2 | 4 |
| Cl⁻ (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 |
| HCO₃⁻ | 39 | 37 | 31 | 29 |
| PCO₂| 33 | 36 | 41 | 38 |
| Na⁺ (mmol/L) | 52 | 48 | 32 |
| K⁺ (mmol/L) | 61 | 58 | 54 |
| Cl⁻ (mmol/L) | 125 | 105 | 88 |

*a; Serum; b; Blood gas analyses; c; Stool

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

**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 Yoshikawa et al. (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 (p.Ile675_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 autosomally recessively. This is the first case report of siblings with the same homozygous mutation in SLC26A3 from Turkey.

Acknowledgement: We would like to express special thanks to Dr. Ayşegül Yılmaz.

Informed Consent: Consent was obtained from the patient’s parent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.D., E.S.; Design - E.S., M.A.G.; Supervision - E.D., E.S.; Funding - E.D., E.S., M.A.G., S.E.; Materials - E.D., M.A.G.; Data Collection and/or Processing - S.E., N.Y.; Analysis and/or Interpretation - E.D., E.S.; Literature Review - M.A.G., N.Y.; Writing - E.S., N.Y.; Critical Review - S.E., N.Y.; Other - E.D., E.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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