

Case Report on a Rare Disease in Lithuania: Congenital Chloride Diarrhea

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Abstract

Keywords

- congenital chloride diarrhea
- *SLC26A3* gene
- chloride malabsorption
- necrotizing enterocolitis

Congenital chloride diarrhea (CCD) is a rare disease, manifesting with secretory diarrhea and life-threatening electrolyte imbalance during infancy. The early diagnosis of CCD is therefore necessary for the adequate treatment. The long-term prognosis of properly managed CCD is favorable. We present a case of complicated CCD with necrotizing enterocolitis. The child was born to nonconsanguineous parents of Lithuanian origin. CCD was suspected due to watery diarrhea, progressive hypochloremia, and high fecal chlorides. Despite oral electrolytes being prescribed, volvulus of small intestine developed requiring several surgical interventions. The clinical diagnosis of CCD was confirmed by molecular genetic testing of *SLC26A3*, which revealed two Polish founder mutations in the DNA of the patient. The prevalence of CCD in Lithuanian neighbor Poland is approximately 1 in 200,000 live births. This is the first described case of CCD in Lithuania to our knowledge, leading to the suggestion that this disease may be underdiagnosed.

Introduction

Congenital chloride diarrhea (CCD) is rare autosomal recessive genetic disease, characterized by chloride malabsorption in the digestive tract. It is caused by pathogenic mutations in the *SLC26A3* gene, which encodes a transmembrane $\text{Cl}^-/\text{HCO}_3^-$ exchanger.¹ To our knowledge, only approximately 250 cases have been reported in the literature.² This disorder is more frequent in Saudi Arabia and Kuwait ($\frac{1}{3}$ in 200–13,000 newborns), Finland (1/30,000–40,000), and Poland (1/200,000).³ The prevalence of CCD in Lithuania is not established. Massive chloride loss in the feces results in profuse watery diarrhea, the main symptom of CCD, and hypochloremic metabolic alkalosis. Biochemical findings are characterized not only by hypochloremia but also by decreased levels of sodium and potassium.²

A flatulent abdomen may be obvious in a newborn and sometimes dilated bowel can be seen on fetal ultrasound. Management of CCD is based on the correction of fluid and electrolyte balance; in newborns, it should be intravenous, while in older patients oral NaCl and KCl solutions are used.² The long-term prognosis of properly managed CCD is favorable.⁴

Case Report

Here we present a case of complicated CCD with small intestine volvulus and consequential mechanical ileus with necrotizing enterocolitis. The patient was born to a non-consanguineous couple following their third pregnancy, which was characterized by polyhydramnios. The fetal ultrasound at 29 weeks gestation detected bloated intestinal

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loops. The male child was born by vaginal delivery at 33 gestational weeks because of chorioamnionitis. His birth weight was 2650 g, and Apgar scores were 8 at 1 minute and 9 at 5 minutes. A distended abdomen with contours of bloated intestinal loops was observed immediately after birth. Intravenous glucose containing fluid was prescribed due to a suspected congenital intestinal anomaly. However, radiography of the abdomen did not reveal any congenital malformation of the intestines, so breast milk feeding was started. Following introduction of oral feeds, the stools were watery and yellowish occurring 8 to 10 times/day, meconium was absent and regurgitation with partly digested milk was observed (►Fig. 1). Biochemical findings included worsening metabolic alkalosis, progressive hypochloremia, hyponatremia, and hypokalemia with no inflammation markers (►Table 1). The neonate was tested for Hirschsprung's disease, cystic fibrosis, and inherited metabolic disorders—all tests were negative. At 17 days of age, congenital chloride diarrhea was suspected because of a high fecal chloride concentration (>90 mmol). The management was adapted to the new diagnosis with enteral feeding and electrolyte infusions correcting blood chloride and potassium. At 34 days of age per oral NaCl and KCl solutions were prescribed (6 mmol/kg Cl ions/day). The pH balance and electrolyte concentrations remained stable and stools were less frequent (4–5/day), although they remained watery. The patient was discharged with oral electrolyte replacement and weekly testing of Cl, Na, K, and pH.

The patient was hospitalized in a severe condition at 2 months of age because of an acute abdomen with profuse watery diarrhea and absence of peristalsis (►Fig. 2). Emer-



Fig. 1 The feces of the infant.

Table 1 Infant blood electrolyte values and pH

	Day			
	1	8	17	34
Na (mEq/L)	133	124	129	140
K (mEq/L)	5.4	4.9	3.2	4.7
Cl (mEq/L)	102	80	87	107
pH	7.44	7.49	7.50	7.37



Fig. 2 The patient at 2 months of age.

gency laparotomy revealed volvulus of the small intestine, requiring the ileum and half of the jejunum to be resected and an enterostoma was formed. The condition was complicated because of necrotizing enterocolitis, so surgery was required on a further four occasions ultimately leaving only 50 cm of jejunum. During this period, the patient had sepsis five times, but serum electrolyte levels remained stable; therefore, no correction was needed. At 4 months of age, the intestinal passage was restored and the child was discharged.

Patient was hospitalized again after 5 days because of severe dehydration, electrolyte imbalance (hypokalemia, hyponatremia), and profuse diarrhea (14–20 times per day). The child was prescribed electrolyte solutions intravenously and orally, diarrhea was treated with cholestyramine, butyrates, diet correction (lactose free formula, thick cereals), and then parenteral nutrition was started. The child's condition slowly improved, and at 7 months of age the child was discharged with daily oral electrolyte solutions.

To confirm clinically suspected CCD the patient and both his parents were tested for mutations in *SLC26A3*. This was by direct sequencing of PCR products of *SLC26A3* exons and splice junctions. The genetic testing was performed in France, at Laboratoire de Biologie Moléculaire, Hôpital de la Conception, Assistance Publique Hôpitaux de Marseille. Two different pathogenic mutations (c.344delT and c.2024_2026dupTCA) in heterozygous state were detected in *SLC26A3* of the patient. The father was found to carry c.344delT, and the mother c.2024_2026dupTCA.

At 10 months of age, the patient's condition remained stable with oral electrolyte replacement and monthly assessment of Cl, Na, and K concentration. He still had six to eight stools daily.

Discussion

The clinical suspicion of CCD could be missed because of the rarity of this disease. The prevalence of CCD in Lithuania might be expected to be somewhat similar to the prevalence of this disease in Poland due to the close historical relationship. This assumption was supported by the results of *SLC26A3* testing in our patient, since both of the detected mutations are described in the literature as Polish founder mutations.^{5–7} c.344delT (p.I115TfsX19) is a frameshift

mutation, resulting in the translation of truncated SLC26A3 protein.⁸ c.2024_2026dupTCA (p.I675dup) results in the frame addition of an isoleucine and production of protein with disrupted function.⁸ The parents of the patient were confirmed as the carriers of these mutations; however, both of them were Lithuanian. Therefore, CCD could be underdiagnosed in Lithuania since this is the first described case of CCD in our country to our knowledge.

Since CCD is a life-threatening disease during infancy because of severe dehydration and electrolyte imbalance, the early diagnosis of this disease is essential. Our experience demonstrates that congenital chloride diarrhea is a relevant diagnosis in Lithuania and should be included in differential diagnosis of watery stool in infancy. Fecal chloride concentration is the best way of differentiating CCD from other conditions.⁹ However, molecular genetic testing of *SLC26A3* should be performed for the confirmation of the clinical diagnosis, especially if the patient condition remains unwell despite adequate treatment.⁷ The prevalence of CCD in Lithuania needs further analysis.

In addition to CCD, the child had volvulus and necrotizing enterocolitis. The pathogenesis of necrotizing enterocolitis differs from CCD which is a genetic disorder. The pathogenesis of necrotizing enterocolitis is characterized by intestinal inflammation that can progress to necrosis and systemic infection, inflammation, multiorgan failure, and sometimes death. Intestinal immaturity and microbial dysbiosis lead to a compromised intestinal epithelial barrier, an underdeveloped immune defense, and altered vascular development and tone. Newborn microbiota can be shaped by formula feeding, antibiotic exposure, and Cesarean delivery and these changes can lead to a compromised intestinal epithelial barrier and progression of intestinal inflammation.¹⁰ Necrotizing enterocolitis typically occurs in the second to third week of life. In this case it was diagnosed at 2 months, in an infant who was fed with human milk and was born by vaginal delivery but had symptoms of CCD from birth. The diagnosis of necrotizing enterocolitis was proven by histology. The only similarity with CCD etiology is that both are more common in premature infants. Newborns with CCD are often premature because intrauterine diarrhea leads to polyhydramnios. CCD causes persistent secretory diarrhea without intestinal inflammation and it starts immediately after birth. Also,

Lundkvist et al explained intermittent abdominal distension in CCD because of intermittent mesenteroaxial twisting of the intestine predisposing some patients to volvulus and malrotation.¹¹ Al Awadhi et al hypothesize this may be related to electrolytes imbalance.¹² The relationships between CCD and necrotizing enterocolitis in this case may also be a coincidence.

Conflict of Interest

None declared.

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