Congenital chloride diarrhea: A rare cause of recurrent polyhydramnios

Jisha Mathew, B S Chandrakala, A Shashidhar, P N Suman Rao

From Department of Neonatology, St. John's Medical College and Hospital, Bengaluru, Karnataka, India

Correspondence to: Dr. Jisha Mathew, #7, 19/1, 9th Cross, Maruthinagar, Madiwala, Bengaluru – 560 068, Karnataka, India. Phone: +91-8025522260/+91-9886546247. E-mail: jishamathew@live.com

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ABSTRACT

Congenital chloride diarrhea (CCD) is a rare, inherited disorder. Our case was a preterm neonate who presented with severe watery diarrhoea since Day 2 of life. There was maternal history of polyhydramnios and dilated bowel loops. The diagnosis of CCD was confirmed by mutation analysis. The infant is 9 months corrected age, on salt and potassium supplementation, with age-appropriate milestones. The diagnosis of CCD must be made early to prevent life-threatening fluid and electrolyte imbalance.

Key words: *Antenatal polyhydramnios, Prematurity, Urine like stools*

Congenital chloride diarrhea (CCD) also known as "Darrow-gamble syndrome" was first described in 1945. It is a rare disorder of intestinal chloride reabsorption with autosomal recessive inheritance. There are only 2 case reports of this disease from India in the early 90's. We present a neonate who was diagnosed to have CCD, currently on salt replacement therapy and with regular follow-up.

CLINICAL BRIEF

Our patient was a preterm baby girl born to a 21 year old mother. There was history of third degree consanguineous marriage. The first pregnancy was a preterm vaginal delivery with antenatally detected polyhydramnios and dilated bowel loops in the fetus. The baby succumbed to illness on the day 1 of life, without any evaluation. The second pregnancy was a medical termination, and the third was a spontaneous abortion at 3 months. This was her fourth pregnancy. She had no medical problems; however, her second-trimester ultrasound scans showed a similar picture of polyhydramnios (amniotic fluid index - 30) with persistent dilated bowel loops. In view of recurrence of similar antenatal ultrasound findings of polyhydramnios and dilated bowel loops, a possibility of cystic fibrosis, CCD, and ileal atresia was considered. Fluorescence *in situ* hybridization for aneuploidy (13, 18, and 21 sex chromosomes) and karyotype from amniotic fluid was normal.

The neonate was born by normal vaginal delivery at 33 weeks of gestation with a birth weight of 2.720 kg. She was noticed to have flaky yellow vernix possibly due to *in utero* diarrhea. The abdomen appeared distended and tense; however, X-ray abdomen ruled out intestinal obstruction and she passed meconium by 6 h of life. Other systemic examination was normal. The baby was noticed to have watery diarrhea on day 2, initially mistaken for urine, as the diarrhea was very watery. By day 4, she had 20% weight loss and severe dehydration. She received IV correction for dehydration. Stool volume was replaced.

At this point, blood investigations showed sodium (Na+): 130, potassium (K+): 6, and chloride (Cl−): 90 (meq/l). Total/Direct bilirubin : 17.86/0.44 , Serum Creatinine 3.4, Blood Urea Nitrogen : 143 (mg/dl). ABG showed metabolic alkalosis. She continued to have ongoing watery stools. Investigations on day 6, Na+: 123, K+:5.15, Cl-: 78 (meq/l). Fecal chloride was 49 mmol/l. A working diagnosis of CCD was made, considering antenatal ultrasonography findings, sibling death with a similar picture, profound watery diarrhea, hypochloremia, hyponatremia, metabolic alkalosis, and elevated fecal Cl^- levels. Targeted gene sequencing detected a homozygous missense variation in exon 3 of the *SLC26A3* gene (chr7:107434271; A>G; Depth: 109×) that results in the amino acid substitution of arginine for tryptophan at codon 63 (p.Trp63Arg). The same variation was detected in heterozygous condition in the parents, indicating that they are asymptomatic carriers of the variant. This is a previously unreported variant in the causative gene, which confirmed the diagnosis.

In view of ongoing losses, NaCl, as table salt, and KCl, as potassium chloride syrup, were added to make up for the need for chloride 6–8 mmol/kg/day, once dyselectrolytemia was controlled. After dehydration was corrected, she was managed on direct breastfeeds+160 ml/kg/day and replacement of stool volume as palladai feeds.

At discharge, blood gas analysis and electrolytes were within normal limits. She continued to have ongoing watery diarhhoea but was gaining weight and passing urine adequately. She was discharged on breastfeeds and measured palladai feeds. The mother was educated regarding the signs of dehydration, the need of frequent follow-up, and regular blood tests. Currently, she is 11 months (CGA-9 months), weighs 9 kg, and on regular

follow-up. Her electrolytes were monitored weekly, then once in 2 weeks, and now monthly, and doses of NaCl and KCl have been adjusted. She has watery stools but of lesser volumes.

DISCUSSION

CCD (online Mendelian inheritance in man 214700) is a rare disorder, reported first in Finland. Most of the 250 reported cases arise from Finland, Poland, and Arab countries [1]. It occurs due to mutations in the SLC26A3 gene which leads to a disorder of intestinal Cl^-/HCO3 exchange at the brush border epithelium of ileum and is characterized by persistent chloride diarrhea. Onset of this illness is *in utero*, with watery diarrhea causing polyhydramnios and triggering preterm labor [2]. Prenatal ultrasonographic diagnosis has been described. Polyhydramnios and massively dilated bowel loops with normal appearance of stomach may suggest CCD rather than intestinal obstructive diseases.

CCD is characterized by lifelong watery, urine like diarrhea. These neonates pass soft watery stool resulting in significant weight loss and dehydration. They also develop a large and distended abdomen with visible bowel loops which sometimes results in a clinical suspicion of intestinal obstruction leading to a surgical exploration. Blood investigations show metabolic alkalosis, hypochloremia, hyponatremia, hypokalemia, hyperaldosteronism, and hyperreninemia [1]. Our neonate had all the above typical clinical and laboratory findings. Nephrocalcinosis and impaired renal function have been reported [3,4]. Wedenoja *et al*. showed that despite the protective renal effect of salt substitution during childhood, the incidence of renal injury in treated CCD is high [3]. Screening renal ultrasound of this neonate showed mildly echogenic kidneys.

Stool pH usually between 4 and 6 and fecal chloride content of >90 meq/l (when serum Cl^- levels are normal) with typical clinical picture are diagnostic. Excessive volume and salt depletion reduce the amount of diarrhea and may result in a low fecal Cl^- of even 40 mmol/L, as is seen in our neonate when serum chloride was low [5]. Definitive diagnosis is by genetic tests. The basic defect of intestinal reabsorption has no definitive treatment. Initial treatment of fluid depletion and salt substitution therapy with NaCl and KCl forms the mainstay of treatment [6]. The optimal dose of chloride varies between 6 and 8 mmol/kg/day in neonates and smaller doses of 3–4 mmol/kg/day are sufficient in older infants to maintain normal serum Cl^- levels [1,5,7,8]. Ketoprofen, omeprazole, oral butyrate, and cholestyramine have been tried [9,10], but our neonate had normal blood gases, electrolytes, and correction of dehydration with just salt and volume replacement.

CONCLUSION

Appropriate replacement therapy started in the neonatal period prevents fatal dyselectrolytemia and dehydration and enables normal physical and mental development in CCD.

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