

Improvement Of Congenital Chloride Diarrhea With Corticosteroids: An Incidental Finding

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Abstract: Congenital chloride diarrhea of infancy is a life threatening disease. We discuss two boys with congenital chloride diarrhea over a long time period before and after kidney transplantation. In the first case, prenatal sonography revealed polyhydramnios and generalized bowel loop distention. The genetic study confirmed congenital chloride diarrhea of infancy. Multiple episodes of severe dehydration, hyponatremia and acute tubular necrosis were seen during the follow up period. He underwent a year of hemodialysis before kidney transplantation. Three periods of improvement concerning diarrhea occurred with the use of corticosteroids, taken for other reasons. These improvements were seen after prednisolone administration for mastoiditis and following prednisolone administration for kidney transplantation. The second case was a 3.5 year old boy who is the cousin of the first case. He was referred to hospital with chronic watery diarrhea, metabolic alkalosis, hypokalemia, hyponatremia and failure to thrive in the first year of life. He was also treated with prednisolone and showed significant improvement.

Keywords: bowel, congenital chloride diarrhea, corticosteroid therapy, hyponatremia, kidney

Introduction And Aim

Congenital chloride diarrhea is a secretory diarrhea which was described by congenital alkalosis and diarrhea.¹ Congenital chloride diarrhea may lead to kidney transplantation.² Slightly preterm birth and lack of meconium and abdominal distention are other hallmarks of the disease and may result in unnecessary surgery.^{3,4}

Classical treatment is oral as well as intravenous replacement of NaCl and KCl.² New treatments include proton pump inhibitor,⁵ captopril,⁶ and cholestyramine.² Incidental improvements of congenital chloride diarrhea was seen in two cases following corticosteroid administration for other reasons. These improvements are reported here and may be beneficial for future studies. There was no published report about the effect of corticosteroids in children with congenital chloride diarrhea.

Case Presentation

Case 1

A seven-year-old boy with low socioeconomic status and a diagnosis of congenital chloride diarrhea is reported here. Diagnosis was made about seven months of age when he was admitted due to repeated episodes of vomiting and diarrhea. He was the first child and his parents were cousins. His birth weight was 2000 gram.

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His mother had several perinatal sonographies. In the first, a live embryo with normal fetal heart rate was seen. Gestational age according to CRL was estimated about seven weeks and 0 day \pm 1 week.

In another perinatal sonography, carried out between 30 and 32 weeks of gestation, the bowel loops were distended generally with pressure effects on kidney and liver of the fetus. In this sonography anal atresia was suggested by the radiologist (Figure 1).

In the last perinatal sonography, the findings were compatible with 38 weeks of gestation and the amniotic fluid was more than normal. Fetal small bowel loops were distended and fluid filled.

The patient had chronic diarrhea from the neonatal period until he was referred to our hospital with severe dehydration seven-months-old. Venous blood gas showed

metabolic alkalosis. Urinary chloride was 5 meq/L. The results of the work-up showed negative findings in term of Barter syndrome. Blood pressure was normal during a follow up. Cystic fibrosis work-up was also done. Result of sweat chloride test and fecal elastase was negative. Stool fat was also negative. There was no history of salty sweet according to the report of the mother.

According to history and laboratory findings, congenital chloride diarrhea was suggested as a clinical diagnosis and we confirmed it with whole exome sequencing. The SLC26A3 mutated gene was evaluated by whole exome sequencing. PCR sequencing was used for confirmation.

The father was a carrier of SLC26A3:CD579 CGA>TGA/N (Arg>Term). The mother was a carrier of SLC26A3:CD579 CGA>TGA/N (Arg>Term).

The child was affected with genotype SLC26A3:CD579 CGA>TGA(Arg>Term)/CD579CGA>TGA (Arg>Term).

The patient was discharged with a normal condition, normal serum creatinine but continues passing watery stools. Renal cortical scintigraphy showed decreased size and function of the right kidney (Figure 2).

He had frequent admissions due to severe dehydration, hyponatremia and acute tubular necrosis. Treatment started at seven months of age with omeprazole, potassium chloride supplement and oral rehydration solution, but these therapies could not decrease his frequent watery diarrhea. Renal function decreased gradually due to several events of acute tubular and cortical necrosis.

He underwent a year of hemodialysis before kidney transplantation (KTP) at eight-years-old. Three periods of improvement concerning the episodes of diarrhea occurred with the use of corticosteroids, administered for other reasons. About four



Figure 1 Distention of the bowel loop was seen in prenatal sonography.



Figure 2 A DMSA scan showed decreased uptake in the right kidney.

months before KTP, the patient received several doses of dexamethasone as a part of the treatment for mastoiditis. The instances of watery diarrhea that occurred more than 10 times a day reduced to less than five times a day, with more consistency. His appetite also increased. The patient's weight increased by about one kilogram in two weeks. After discontinuing the dexamethasone, the bowel habit worsened again.

The second period of improvement in the instances of diarrhea happened after the administering of prednisolone for immunity suppression after KTP. The patient gained about 6 kg in the first two months with a good graft function. Tapering of prednisolone (less than 0.5 mg/kg) in 4th month, increased the frequency of watery stool passing. In month five post-KTP, the patient was referred with severe dehydration and acute renal failure (creatinine: 5.2 mg/dl) and received methylprednisolone as part of treatment for acute rejection. The stool passing decreased and the boy left hospital with normal renal function.

Case 2

The cousin of the previous case has the same problem. He is a 3.5-year-old boy. He was referred to hospital with chronic watery diarrhea, metabolic alkalosis, hypokalemia, hyponatremia and failure to thrive in the first year of life. The patient was born with 2000gr from a consanguineous marriage. His mother had polyhydramnios in the prenatal period. In early evaluation we found hypochloremia (70 mmol/L) with decreased urine chloride (1 mmol/L) and normal sweat chloride test. We treated the patient as a congenital chloride diarrhea with omeprazole, potassium chloride supplement and oral rehydration solution. These treatments were successful for the fluid and electrolyte abnormalities but the chronic diarrhea continued. After improvements in the episodes of diarrhea with corticosteroids in the previous case, the parents asked us to use this drug as a trial for this child. So we started 1.5 mg/kg prednisolone in two doses and after a month the patient showed significant improvement in stool passing from more than 15 occurrences of watery diarrhea a day to less than five with more consistency.

Discussion

Congenital chloride diarrhea was first described by Darrow⁷ and Gamble¹ as Darrow Gamble disease. This condition manifests as watery diarrhea that contains more chloride than sodium and potassium and leads to hypochloremic metabolic alkalosis.

Our patients had metabolic alkalosis with low urinary chloride levels. Chloride responsive metabolic alkalosis had

several etiologies: Cystic fibrosis, congenital chloride diarrhea, diuretic therapy, and post hypercapnia metabolic alkalosis.

Congenital chloride diarrhea begins in fetal life. Untreated congenital chloride diarrhea may lead to death in early fetal life.² Congenital chloride diarrhea is caused by mutations in SLC26A3 and inheritance is autosomal recessive.⁸ Polyhydramnios and generalized distended bowel loops were reported in previous cases.⁹⁻¹¹ Our first case had polyhydramnios and generalized loop distention in prenatal ultrasonography.

Generalized distention of bowel loops suggest congenital chloride diarrhea because obstructive lesions tend to create localized distention.¹² Infants who are diagnosed and treated shortly after birth may be able to develop and grow normally.¹³

CCD should be suspected in a child with a prenatal history of polyhydramnios, generalized bowel loop distention, repeated episode of dehydration, and metabolic alkalosis.⁸

Improvement of diarrhea and significant weight gain are interesting phenomena in our cases. In CCD, defective chloride absorption leads to osmotic diarrhea. The metabolic abnormalities are related to absence or impairment of active chloride/bicarbonate exchange in both the ileum and colon.⁹ We cannot explain the mechanism of diarrhea improvement after the use of corticosteroids but we suggest its use in selected cases, and for further study in this context.

However treatment with corticosteroid is not without adverse effects. Adverse effects of long term treatment with corticosteroid such as osteoporosis¹⁴ and obesity¹⁵ should be kept in mind in contrast to other suggested treatments, such as proton pump inhibitor,² butyrate¹⁶ and cholestyramine.¹⁷

In the retrospective cross-sectional study by Hihnala et al, no deaths due to congenital chloride diarrhea were reported after 1972.¹⁸ End-stage renal disease, male subfertility, inguinal hernia, and spermatocele were reported among patients with congenital chloride diarrhea.¹⁸

Limitation

Due to financial problems, genetic analysis was done recently after clinical diagnosis and treatment. Fecal ionogram was not available. We did not use different dosage of glucocorticoid.

Ethical Consideration

No institutional approval was required to publish this case report. Informed consent signed by the parents was obtained.

Disclosure

The authors report no conflicts of interest in this work.

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