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Congenital Chloride Losing Diarrhea

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Abstract

Background: Congenital chloride-losing diarrhea is a medical emergency that become a mostly pediatric problem in many countries including Saudi Arabia. It is requiring early diagnostics and treatment to prevent severe dehydration and infant mortality.

Aim of the review: To summarize data on congenital chloride diarrhea including: incidence, pathophysiology and management.

Methods: Data are based on MEDLINE search for chloride losing diarrhea in addition to clinical experience in treatment of these cases.

Results: Life-long salt substitution with NaCl and KCl stabilizes fluid, electrolyte and acid-base balance. When early diagnosed and properly treated, the long-term outcome is favorable.

Conclusions: This review summarizes data on congenital chloride diarrhea and provides guide lines of treatment.

Keywords: Chloride ions; Diarrhea; Alkalosis

Introduction

Chloride ions play many physiological roles, including regulation of cell volume, fluid secretion, and acid-base balance [1-4].

In 1945, Holmberg et al. and wedejoja et al., [5,6] published reports of two patients presenting with a new syndrome, characterized by watery diarrhea, high content of chloride in the stools, and metabolic alkalosis. The disease was named metabolic alkalosis with diarrhea, or congenital chloridorrhea but when the primary pathology was understood to involve the transport of chloride, in the distal ileum and colon, the disease was renamed as Congenital Chloride Diarrhea (CCD) or Chloride Losing Diarrhea (CLD) [7,8].

Incidence

The disease is particularly frequent in: Kuwait with an incidence of 1/3200 due to a high prevalence of consanguinity marriages in these countries, Saudi Arabia , it was 1st described in 1981 with an incidence of 1/5000, Finland with an Incidence of 1/30,000-40,000, and Poland with an Incidence of 1/200,000 (Figure 1) [6,9].

Single cases with CLD appear worldwide, both in developing and more affluent countries, making diagnostics challenging. If a suspicion of CLD arises, especially in low-incidence countries, mutation analysis may be required to establish the diagnosis [10,11].

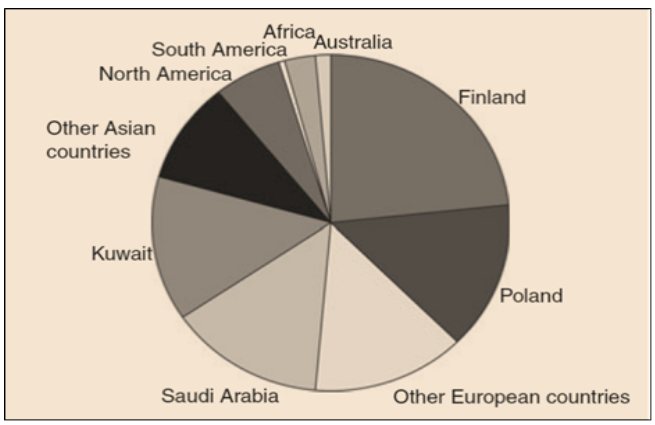

Figure 1: Geographical distribution of reported cases of congenital chloride diarrhea.

Genetics

It is a rare autosomal recessive disorder caused by mutations in the CLD gene called the solute carrier family 26 member 3 gene (SLC26A3 alias DRA), mapped to chromosome 7q31 [6,12]. It encodes for an apical epithelial Cl^-/HCO_3^-exchanger, the intestinal loss of which causes profuse Cl−-rich diarrhea [10,13].

SLC26 gene family encodes anion exchangers capable of transporting a wide variety of monovalent and divalent anions include the chloride, sulfate, bicarbonate, format, oxalate and hydroxyl ions. Three members of the gene family are involved in genetic disease; SLC26A2 in chondrodysplasias, SLC26A3 in chloride-losing diarrhea, and SLC26A4 in Pendred syndrome and hereditary deafness (DFNB4) [14].

Over 30 different SLC26A3 mutations–including the founder mutations of Finland, Poland, and Arabic countries–has been demonstrated to cause CLD [12,15]. In spite of the various types of mutations and their wide distribution in different regions of the SLC26A3 gene, evidence of genotype-phenotype differences remain non-existent [11,15].

Pathophysiology

The mechanisms of diarrhea are generally divided into secretory and osmotic, but often diarrhea is the result of both mechanisms. Secretory diarrhea is usually associated with large volumes of watery stools and persists when oral food is withdrawn. Osmotic diarrhea

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is dependent on oral feeding, and stool volumes are usually not as massive as in secretory diarrhea [16].

SLC26A3 encodes for a trans-membrane protein, which is an apical epithelial (Cl/HCO_3) exchanger [4,6,11,14,17,18]. The basic defect of CLD is loss of the SLC26A3-mediated transport in the surface epithelium of the ileum and colon [19-23] (Figure 3). This results in defective intestinal absorption of Cl and secretion of HCO_3. Secondarily, the coupled epithelial Na^+/H^+ transport through the Na^+/H^+ exchangers (NHE2 and/or NHE3) is defective (Figure 2) [14,22-25] leading to intestinal loss of both NaCl and fluid, and watery Cl-rich diarrhoea. In untreated disease and in the first hour after birth, there will be hypochloremia, hyponatremia, and dehydration which result in activation of the renin-angiotensin system. The above findings together with hydramnios invariably present and meconium lacking is strong evidence of intrauterine diarrhea [5]. The resultant hyperaldosteronism (compensatory mechanism) induces Na+ reabsoprtion in the distal colon and especially in the distal tubule of the kidney, resulting in the secondary K^+ depletion which leads to an increase in both the hypokalemia and metabolic alkalosis in untreated CLD [5,24,26] Therefore, the main laboratory findings in untreated CLD are hypochloraemia, hypokalemia and metabolic alkalosis [26].

It should be noted that, if no treatment is instituted serum Na^+ content rises to normal concentrations [5,26]. The body compensates for the electrolyte disturbance through an increase in the absorption of Na^+ and water in the kidney and intestine at a cost of a loss of K^+ in these organs. The alkalosis probably develops partly through an associated increase in H^+ excretion and partly through an absence of HCO; secretion in the ileum and colon [27].

Clinical Presentation

Antenatally

Affected fetuses develop secretory "urine like" diarrhea [27] (Figure 7) in utero resulting in distended bowel loops and polyhydramnios which leads to premature birth and lack of meconium [6,17]. These abnormalities are visible in ultrasonic investigation Figure 4, even at the end of the second trimester [28,29].

At birth

These infants have markedly distended abdomen and visible peristalsis of bowel loops together with low birthweight (below 2500 g) (Figures 5 and 6). A situation may be mistaken for intestinal obstruction (Figure 6) [5,26,30].

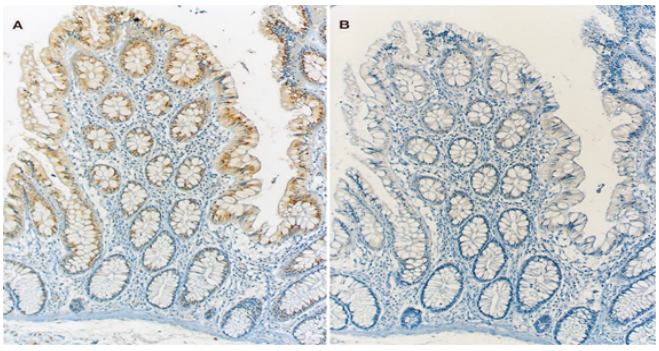

Figure 2: Immunohistochemical staining of the congenital chloride diarrhea (CLD) protein. A.) Normal colon (*left*). B.) Preimmune serum control is also shown (*right*).

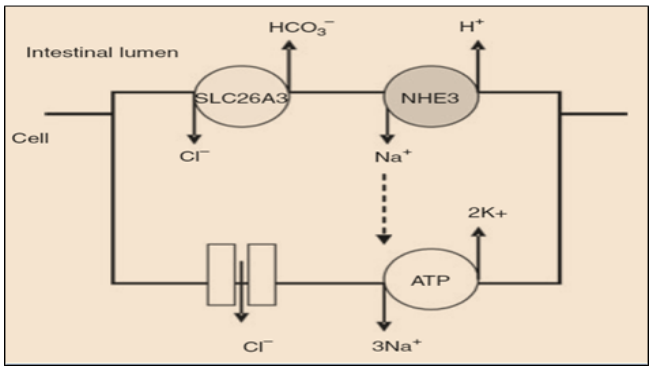

Figure 3: SLC26A3 is coupled with NHE3 in surface epithelial cells of the colon.

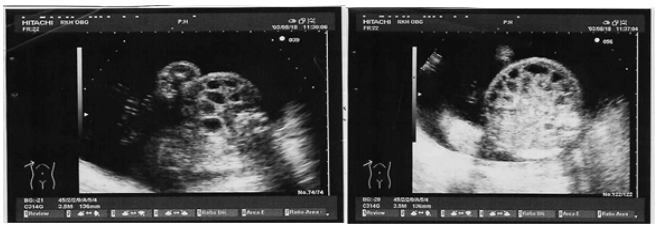

Figure 4: Ultrasound examinations may reveal a regular abdominal distension and dilatation of intestinal loops after 25 weeks.

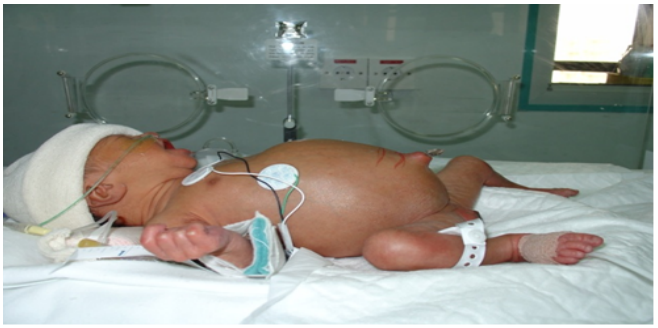

Figure 5: Preterm 34 weeks infant with CLD, noticed the abdominal distension.

Profuse watery diarrhea started immediately soon after birth that may be confused with urine and misdiagnosed as delayed passage of meconium that if not diagnosed early, leads to unnecessary surgical interventions. (Figure 6) [23,31,32].

In the first days of life severe dehydration develops that is usually iso-osmolal, but may already then be markedly hypo-osmolal. In inadequately treated infants dehydration will always become hypo-osmolal during the first week.10 Hyponatraemia (serum Na^+ <130 mmol/L) and hypochloraemia (serum Cl) <100 mmol/L) accompanied by metabolic alkalosis, and hypokalaemia develop soon after. This metabolic imbalance together with severe dehydration if not treated properly is usually lethal during the first weeks or months of life [6,20,33].

Diagnosis

Congenital chloride diarrhoea diagnosis in the neonatal period is based on its typical clinical picture and a high concentration of faecal Cl, exceeding 90 mmol/L after correction of the fluid and electrolyte

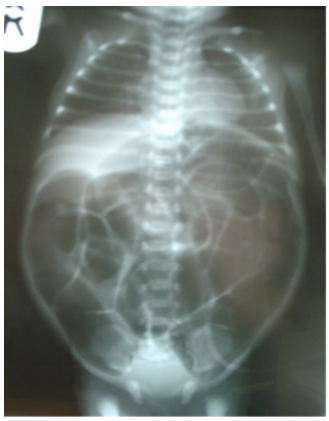

Figure 6: Postnatal radiograph of the abdomen of the above neonate. There is generalized dilatation of the small and large bowel without evidence of mechanical obstruction.

Figure 7: Bag contains urine like diarrhea.

depletion [34]. The typical diagnosis is the unusual association between profuse diarrhea and metabolic alkalosis [27]. It is worth noticing, however, that excessive volume and salt depletion reduces the amount of diarrhoea and may result in a low faecal Cl of even 40 mmol/L [34]. In such cases repeated faecal samples are needed for diagnostics. After 3 months of life CLD is diagnosed by higher fecal chloride concentration than the sum of the fecal sodium and potassium concentrations. Although genetic testing for CLD is possible, the simple measurement of faecal Cl is still sufficient to confirm the diagnosis in most of the cases together with water stool with pH between 4 and 6 [6,34,35].

Some cases remain undiagnosed in early infancy and survive, like the proband, have a chronic course of the disease with persistent hypovolemia and hypo electrolytemia that leads to growth retardation. Older patients with an undiagnosed and/or untreated disease tend to present more variation in their clinical picture as dietary compensation, such as consumption of salt, varies between patients. Acute worsening of the clinical condition may follow common infections or vomiting. The proband was diagnosed as having CLD at the age of five years after a long period of chronic diarrhoea of unknown origin. Thereafter, compliance with electrolyte and fluid substitution was poor, inhibiting normal growth. In the long term, chronic contraction of the intravascular space predisposes these patients to complications such as renal impairment and gout [25].

Complications

Diarrhea & fecal incontinence

The diarrhoea of CLD is life-long. In the Finnish series, the amount of stools per day ranged from 2 to 7 L/d. As a result of the watery content of stools, a common problem in children with CLD is soiling. Only minor soiling problems, occurring during the night-time or during physical exertion, remain in adulthood [36].

Renal injury

Renal injury is the major complication of inadequate therapy during childhood. Chronic hypovolemia itself causes a series of secondary effects. An increase in renin and angiotensin concentrations, with secondary hyperaldosteronism, results in vascular changes in the kidney resembling those seen in hypertension, even when these patients have normal blood pressure [37]. Chronic potassium depletion results in impaired functioning of renal tubular and intestinal absorptive cells [37,38].

Male subfertility

As the SLC26A3 protein is expressed in several tissues of the male reproductive tract, a probable mechanism for subfertility is the disrupted SLC26A3-mediated anion exchange [6]. It involves a low concentration of poorly motile spermatozoa with abnormal morphology, and a high seminal plasma Cl with a low pH, resembling the intestinal electrolyte and acid-base imbalance of CLD [18]. Another unique phenotype in adult males, large bilateral spermatoceles, gives further support to the role of defective salt and water reabsorption in the male reproductive tract [6,18].

Hyperuricaemia & gout

Congenital chloride diarrhoea seems to be associated with an age-dependent increasing risk for hyperuricaemia [18].

Sweat gland

The increased concentrations of sweat Cl in patients with CLD, similar to that seen in patients with cystic fibrosis, suggest a minor role for SLC26A3 in the sweat gland. Adding salt substitution during excessive sweating may thus be necessary [39].

Management

Salt substitution therapy with NaCl and KCl

In early neonatal period, the amounts of NaCl and KCl in substitution therapy are added to intravenous maintenance fluids, as follows 120-300 mL/day (patients aged 0-7 days), 500-700 mL/day (patients aged more than 7days). Administration of salt substitution is gradually changed from intravenous to peroral therapy with 3–4 daily doses.

In infancy, the substitution is dilution of 0.7% NaCl and 0.3% KCl, whereas after the three first years of life, more concentrated solution of 1.8% NaCl and 1.9% KCl are recommended. The optimal dosage of Cl ranges from 6 to 8 mmol/kg/day in infants and from 3 to 4 mmol/kg/day in older patients [6,10].

The rationale: Salt substitution increases intestinal absorption by unspecified mechanisms and inhibits development of hypochloraemic and hypokalaemic metabolic alkalosis. Despite the therapy, the defective SLC26A3-mediated anion transport remains in the intestine and the diarrhoea is persistent. Although the relative amount of stools decreases with age, intestinal loss of electrolytes, and especially that of Cl, is continuous. If the dosage of salt substitution is insufficient, hypochloraemia and active reabsorption of Cl both in the distal colon and in the distal nephron result in Cl-free urine. Accordingly, adequate

excretion of Cl into the urine, in addition to normal electrolyte and acid-base status, confirms the sufficiency of salt substitution [15].

Proton pump inhibitor

Treatment with omeprazole was associated with reductions in the volume and frequency of stools and the cessation of incontinence in cases of CLD [33]. This improvement was due to the inhibition of gastric chloride secretion, which should not only protect endogenous chloride stores but also reduce the amount of chloride presented to the intestine, thereby reducing the amount of unabsorbed chloride in the stool and reducing the cations and water that need to be excreted to maintain electrical and osmotic equilibrium. However, this treatment does not reduce the need for careful monitoring of dietary intake, serum electrolyte concentrations, and urinary chloride excretion [40].

Oral butyrate

The short-chain fatty acid butyrate could be effective in treating congenital chloride diarrhea. It is easily administered, useful in preventing severe dehydration episodes, and may be a promising therapeutic approach for a long-term treatment in this rare and severe condition [37].

It stimulates intestinal water and ion absorption through a variety of mechanisms, including the activation of a parallel Cl_/butyrate and Na_/H_ exchanger. In addition, it has been shown that butyrate is also able to inhibit both basal and adenosine 3_,5_-cyclic monophosphate–stimulated Cl_ secretion in a dose-dependent manner [41]. Finally, the trophic effects elicited by short chain fatty acids on intestinal mucosa (mediated through circulatory, hormonal, and neural mechanisms) could contribute to improvement in diminishing severity of diarrhea in the CLD patient [37,41].

Cholestyramine

It binds bile acids and reduces intestinal secretion, resulting in a moderate reduction in diarrhoea for two to 4 weeks. In children, short courses of cholestyramine (dose 2g/day) can be used to temporarily reduce the diarrhoea and prevent soiling [41,42].

Outcome

During the last 40 years, CLD has been changed from a mostly fatal disorder to a treatable disease with an established genetic basis. Prompt recognition and adequate replacement of fecal loss of chloride, sodium, potassium, and water are mandatory for satisfactory disease outcome [43].

References

1. Charney AN, Feldman GM (1984) Systemic acid-base disorders and intestinal electrolyte transport. Am J Physiol 247: G1-12.
2. O'Neill WC (1999) Physiological significance of volume-regulatory transporters. Am J Physiol 276: C995-995C1011.
3. Barrett KE, Keely SJ (2000) Chloride secretion by the intestinal epithelium: molecular basis and regulatory aspects. Annu Rev Physiol 62: 535-572.
4. Hayashi H, Suruga K, Yamashita Y (2009) Regulation of intestinal Cl-/HCO3- exchanger SLC26A3 by intracellular pH. Am J Physiol Cell Physiol 296: C1279-1290.
5. Holmberg C, Perheentupa J, Launiala K, Hallman N (1977) Congenital chloride diarrhoea. Clinical analysis of 21 Finnish patients. Arch Dis Child 52: 255-267.
6. Wedenoja S, Pekansaari E, Höglund P, Mäkelä S, Holmberg C, et al. (2011) Update on SLC26A3 mutations in congenital chloride diarrhea. Hum Mutat 32: 715-722.
7. Darrow DC (1945) Congenital alkalosis with diarrhoea. J Pediatr 426: 519-532.
8. Gamble JL, Fahey KR, Appleton J, MacLachan E (1945) Congenital alkalosis with diarrhoea. J Pediatr 26: 509-518.
9. Höglund P, Auranen M, Socha J, Popinska K, Nazer H, et al. (1998) Genetic background of congenital chloride diarrhea in high-incidence populations: Finland, Poland, and Saudi Arabia and Kuwait. Am J Hum Genet 63: 760-768.
10. Höglund P, Haila S, Socha J, Tomaszewski L, Saarialho-Kere U, et al. (1996) Mutations of the Down-regulated in adenoma (DRA) gene cause congenital chloride diarrhoea. Nat Genet 14: 316-319.
11. Mäkelä S, Kere J, Holmberg C, Höglund P (2002) SLC26A3 mutations in congenital chloride diarrhea. Hum Mutat 20: 425-438.
12. Norio R, Perheentupa J, Launiala K, Hallman N (1971) Congenital chloride diarrhea, an autosomal recessive disease. Genetic study of 14 Finnish and 12 other families. Clin Genet 2: 182-192.
13. Moseley RH, Höglund P, Wu GD, Silberg DG, Haila S, et al. (1999) Downregulated in adenoma gene encodes a chloride transporter defective in congenital chloride diarrhea. Am J Physiol 276: G185-192.
14. Dorwart MR, Shcheynikov N, Baker JM, Forman-Kay JD, Muallem S, et al. (2008) Congenital chloride-losing diarrhea causing mutations in the STAS domain result in misfolding and mistrafficking of SLC26A3. J BiolChem 283: 8711-8722.
15. Dechant MJ, Wedenoja S, Höglund P, Prange-Schmidt S, Zimmer KP, et al. (2012) Follow-up of a child with congenital chloride diarrhoea caused by a novel mutation. ActaPaediatr 101: e256-259.
16. Nuki G, Watson ML, Williams BC, Simmonds HA, Wallace RC (1991) Congenital chloride losing enteropathy associated with tophaceous gouty arthritis. AdvExp Med Biol 309A: 203-208.
17. Schweinfest CW, Spyropoulos DD, Henderson KW, Kim JH, Chapman JM, et al. (2006) slc26a3 (dra)-deficient mice display chloride-losing diarrhea, enhanced colonic proliferation, and distinct up-regulation of ion transporters in the colon. J BiolChem 281: 37962-37971.
18. Hihnala S, Kujala M, Toppari J, Kere J, Holmberg C, et al. (2006) Expression of SLC26A3, CFTR and NHE3 in the human male reproductive tract: role in male subfertility caused by congenital chloride diarrhoea. Mol Hum Reprod 12: 107-111.
19. Launiala K, Perheentupa J, Pasternack A, Hallman N (1968) Familial chloride diarrhea-chloride malabsorption. BiblPaediatr 87: 137-149.
20. Turnberg LA (1971) Abnormalities in intestinal electrolyte transport in congenital chloridorrhoea. Gut 12: 544-551.
21. Bieberdorf FA, Gorden P, Fordtran JS (1972) Pathogenesis of congenital alkalosis with diarrhea. Implications for the physiology of normal ileal electrolyte absorption and secretion. J Clin Invest 51: 1958-1968.
22. Pearson AJ, Sladen GE, Edmonds CJ, Tavill AS, Wills MR, et al. (1973) The pathophysiology of congenital chloridorrhoea. Q J Med 42: 453-466.
23. Khan SN, Yaish HM (1992) Misdiagnosis of congenital chloride-losing diarrhea. J Perinatol 12: 112-114.
24. Kere J, Lohi H, Höglund P (1999) Genetic Disorders of Membrane Transport III. Congenital chloride diarrhea. Am J Physiol 276: G7-7G13.
25. Jenkins H R, Milla P J (1997) Congenital Chloride-Losing Diarrhoea: Absence of the Anion-Exchange Mechanism in the Rectum. Journal of Pediatric Gastroenterology & Nutrition 24: 518-521.
26. Wedenoja S, Höglund P, Holmberg C (2010) Review article: the clinical management of congenital chloride diarrhoea. Aliment PharmacolTher 31: 477-485.
27. Parikh BN, Khubchandani RP, Amdekar YK, Ugra D, Patel A, et al. (1993) Congenital chloride diarrhea. Indian Pediatr 30: 811-813.
28. Imada S, Kikuchi A, Horikoshi T, Ishikawa K, Tamaru S, et al. (2012) Prenatal diagnosis and management of congenital chloride diarrhea: A case report of 2 siblings. J Clin Ultrasound 40: 239-242.
29. Kim SH, Kim SH (2001) Congenital chloride diarrhea: antenatal ultrasonographic findings in siblings. J Ultrasound Med 20: 1133-1136.
30. Badawi MH, Zaki M, Ismail EA, Majid Molla A (1998) Congenital chloride diarrhoea in Kuwait: a clinical reappraisal. J Trop Pediatr 44: 296-299.

31. Eğrıtaş O, Dalgiç B, Wedenoja S (2011) Congenital chloride diarrhea misdiagnosed as Bartter syndrome. Turk J Gastroenterol 22: 321-323.

32. Lok KH, Hung HG, Li KK, Li KF, Szeto ML (2007) Congenital chloride diarrhea: a missed diagnosis in an adult patient. Am J Gastroenterol 102: 1328-1329.

33. Aichbichler BW, Zerr CH, Santa Ana CA, Porter JL, Fordtran JS (1997) Proton-pump inhibition of gastric chloride secretion in congenital chloridorrhea. N Engl J Med 336: 106-109.

34. Musch MW, Arvans DL, Wu GD, Chang EB (2009) Functional coupling of the downregulated in adenoma Cl-/base exchanger DRA and the apical Na+/H+ exchangers NHE2 and NHE3. Am J PhysiolGastrointest Liver Physiol 296: G202-210.

35. Li WC, Shih HH, Wu KL, Chou CC (2003) Congenital chloride diarrhea in a child. J Formos Med Assoc 102: 424-428.

36. Lee DH, Park YK (2012) Antenatal differential diagnosis of congenital chloride diarrhea: a case report. J ObstetGynaecol Res 38: 957-961.

37. Wedenoja S, Ormälä T, Berg UB, Halling SF, Jalanko H, et al. (2008) The impact of sodium chloride and volume depletion in the chronic kidney disease of congenital chloride diarrhea. Kidney Int 74: 1085-1093.

38. Al-Hamad NM, Al-Eisa AA (2004) Renal abnormalities in congenital chloride diarrhea. Saudi Med J 25: 651-655.

39. Haila S, Saarialho-Kere U, Karjalainen-Lindsberg ML, Lohi H, Airola K, et al. (2000) The congenital chloride diarrhea gene is expressed in seminal vesicle, sweat gland, inflammatory colon epithelium, and in some dysplastic colon cells. Histochem Cell Biol 113: 279-286.

40. Pieroni KP, Bass D (2011) Proton pump inhibitor treatment for congenital chloride diarrhea. Dig Dis Sci 56: 673-676.

41. Canani RB, Terrin G, Cirillo P, Castaldo G, Salvatore F, et al. (2004) Butyrate as an effective treatment of congenital chloride diarrhea. Gastroenterology 127: 630-634.

42. Holmberg C, Miettinen T, Perheentupa J (1982) Reduction of diarrhea with cholestyramine in congenital chloride diarrhea (CCD). Pediatr Res 16: 702

43. Höglund P, Holmberg C, Sherman P, Kere J (2001) Distinct outcomes of chloride diarrhoea in two siblings with identical genetic background of the disease: implications for early diagnosis and treatment. Gut 48: 724-727.