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Advanced Chronic Renal Failure Due to Occult Congenital Chloride Diarrhea

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Abstract

Background: Congenital chloride diarrhea (CCD) is a rare autosomal recessive disorder of intestinal chloride-bicarbonate (Cl/HCO_3) exchange caused by mutations in the SLC26A3 gene on chromosome 7. It is characterized by persistent chloride (Cl) rich watery diarrhea (>90 mmol/L), low sodium (Na), low potassium (K), and metabolic alkalosis with low urinary Cl and K from birth. Treatment is symptomatic, and replacement therapy with NaCl and KCl has been shown to be effective in children, but its long-term prognosis remains unclear. **The case:** A 17-year-old female patient presented with advanced chronic renal disease. She had persistent watery diarrhea since birth with recurrent admissions for dehydration. Despite hypokalemia and metabolic alkalosis as well as the absence of infectious, autoimmune, and iatrogenic etiologies, the diagnosis of CCD was missed and hydration was limited to emergency admissions. On her last admission with us, she had typical laboratory abnormalities of CCD and the diagnosis was established by high stool Cl. Moreover, it was confirmed by genetic testing. She had bilateral small kidneys at 6 cm and high serum creatinine at 780 μmol/L. She was treated with intravenous NaCl and KCl solutions and subsequently with adequate maintenance oral supplementation. She improved clinically and her serum creatinine decreased to 340 μmol/L 1 month later and remained stable after 2 years of follow-up. **In conclusion:** CCD can lead to intrinsic chronic renal disease if the diagnosis is missed or mistreated.

Keywords

Congenital Chloride Diarrhea, Hypokalemia, Renal Failure

1. Introduction

Congenital chloride-losing diarrhea (CCD) is a rare genetic disorder due to an

autosomal recessive mutation in the SLC26A3 gene on chromosome 7 [1]. The mutation leads to defective intestinal chloride-bicarbonate (Cl-HCO_3) exchanges and epithelial sodium (Na)/hydrogen (H) transport through the Na/H exchangers (NHE2 and/or NHE3), with the resultant intestinal loss of chloride and retention of bicarbonate [2]. Consequently, the renin-angiotensin-aldosterone system is activated, resulting in sodium (Na) reabsorption and potassium (K) excretion, leading to dehydration, hypokalemia, and metabolic alkalosis [3]. The first description of the disease was in 1945 by Gamble and Darrow, and nearly 250 cases have been reported to date [4]. Most of the cases have been reported in children from Finland, with a calculated prevalence of 1 in 43,000 newborns [5]. In the Arab world, only a few cases have been reported in children from Saudi Arabia and Kuwait [6] [7]. The overall long-term prognosis was described as favorable with optimal lifelong Na and K substitution, though complications such as renal disease, gout, inguinal hernias, spermatoceles, and decreased fertility have been rarely reported in noncompliant pediatric patients [8]. Unfortunately, long-term follow-up on such patients, and specifically in adults, is rare. In this case report, we describe an adult female with this rare disease, who almost lost her kidneys due to dietary noncompliance.

2. The Case

A 17-year-old woman presented with progressive nausea and vomiting over a few weeks. Her past medical history revealed multiple admissions with watery diarrhea since birth. Her previous investigations showed low serum as well as urinary Cl, Na, and K. Serum uric acid (UA) and HCO_3 were high. She was treated with a high-salt diet in addition to Slow K and calcium tablets on those occasions only. Moreover, for the past 12 years, she had a few attacks of joint pain with high uric acid (UA), which responded mainly to rehydration and limited NSAID use. On her initial presentation, the patient was conscious, oriented x3, and without distress, shortness of breath, or pain. Blood pressure was 180/110 mmHg. She was afebrile, with a body weight of 54 kg. She did not have jugular venous distension or edema. Systemic examination did not show any abnormality. Her demographic, laboratory investigations, and follow-up data are summarized in **Table 1**. She had normal peripheral leukocyte and platelet counts. Hemoglobin was 93 g/L with normal transferrin saturation % and vitamin B12. Serum urea and creatinine were elevated at 40 mmol/L and 780 μmol/L, respectively. Serum tests revealed low Na, Cl, corrected calcium (Ca), and K at 129, 93, 1.7, and 2.9 mmol/L, respectively. Serum UA was elevated at 700 μmol/L. Liver tests were normal with serum albumin at 41 g/L. Serum cholesterol and TSH were normal. Serum pH was 7.5 and HCO_3 at 32 mmol/L. Urine routine and microscopy were normal. Serum complements (C3 & C4), IgA level, and protein electrophoresis were normal. Anti-CCP, ANA, anti-ds DNA, ANCA, anti-GBM antibodies, hepatitis B surface antigen, and anti-HCV antibodies were negative. Stool tests were negative for ova, parasites, and occult blood. Fecal calprotectin was at a normal level. Stool Cl was

120 mmol/L with very low urinary Na, Cl, and K. Genetic analysis confirmed an SLC26A3 c.269_270dupAA homozygous mutation in exon 3, leading to a frameshift from the 91st amino acid Gly and alteration of the SLC26A3 transmembrane protein sequence. Chest x-ray and ECG were normal. Abdominal and pelvic ultrasound did not show any abnormality except for bilateral small kidneys at 6 cm with thin and echogenic cortex, yet without hydronephrosis or calcifications (Figure 1). She was treated initially with intravenous KCl until K was >4, then with normal saline until establishing an euvolemic state. Subsequently, she was maintained on a high Na and K solution. Moreover, she needed protective medications: omeprazole 20 mg for KCl gastritis, calcium and one alpha for osteoporosis, and allopurinol 300 mg daily for gout, as well as erythropoietin for her renal-hyperproliferative anemia. By 1 month later, she felt better and her electrolytes, UA, and anemia were corrected. At the same time, serum creatinine decreased to 340 μmol/L. By 2 years later, she remained asymptomatic and her serum creatinine was stable at 330 μmol/L.

Table 1. Demographic features and biochemical changes, over time, of a treated patient with congenital chloride-losing diarrhea.

	Time (months)				
	0	1	3	12	24
Clinical data					
uremia	3(+)	(−)	(−)	(−)	(−)
Blood pressure (120 - 80 mmHg)	100/50	120/80	120/80	120/80	120/80
Body weight (kg)	41	47	48	50	52
Laboratory tests					
Serum					
Albumin (35 - 50/L)	49	32	33	36	38
Urea (2.5 - 7.8 mmol/L)	40	19	18	15	16
Creatinine (60 - 120 μmol/L)	780	340	320	312	330
Uric acid (240 - 500 μmol/L)	720	430	390	401	380
Sodium (135 - 150 mmol/L)	129	131	134	135	136
Potassium (3.5 - 5 mmol/L)	2.9	3.1	3.5	3.8	3.9
Chloride (96 - 106 mmol/L)	91	96	98	98	99
Bicarbonate (22 - 29 mmol/L)	32	28	24	25	24
Corrected calcium (2.1 - 2.3 mmol/L)	1.7	2.1	2.2	2.2	2.3
Hemoglobin (120 - 150 g/L)	93	110	112	120	118
Urine analysis					
Albumin/creatinine (<30 mg/g)	29	25	20	23	24
Sodium	8	14	17	17	18
Potassium	6	8	11	15	17
Chloride	6	14	17	16	18

Demographical features: 17-year-old, female; White Presentation: chronic diarrhea and uremia; Kidney US: bilaterally small kidneys; Hyponatremia, hypochloremia, and hypokalemia with metabolic alkalosis and low sodium, potassium, and chloride in urine. Urine protein: negative; Stool chloride: >(120 mmol/L); Negative test for: protozoa, infections, autoimmune diseases. Colonic endoscopy and biopsy: normal.

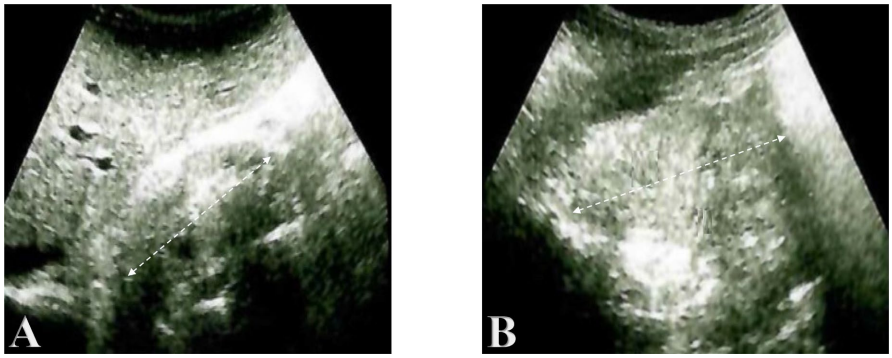


Figure 1. Ultrasonographic pictures of the (A) right and (B) left kidneys of the patient showing bilateral small kidneys at 6 cm with a thin and echogenic cortex, yet without cortical scars, hydronephrosis, and calcifications.

3. Discussion

Chronic diarrhea is defined as the passage of >3 bowel movements per day, regardless of consistency, that lasts >4 weeks [9]. Diarrhea is common in children due to (a) infections, (b) autoimmune disorders and inflammatory bowel diseases, (c) sorbitol-induced (toddler's) diarrhea, (d) antibiotic-associated diarrhea, short bowel bacterial overgrowth, (e) digestive diseases viz. malabsorption syndromes, hepatic diseases, pancreatic insufficiency with/without cystic fibrosis, (f) genetic disorders viz. congenital disaccharidase deficiency, abetalipoproteinemia, enteric anendocrinosis, acrodermatitis enteropathica (zinc malabsorption), and chronic sodium diarrhea, (g) motility disorders (Münchausen's syndrome) [9]. However, diarrhea associated with metabolic alkalosis is limited to CCD and microvillous inclusion disease. Patients with CCD have chronic watery diarrhea with high fecal Cl (>90 mmol/L), low K, and metabolic alkalosis with low urinary Cl and K [5]. Diagnosis is usually suspected with fetal abdominal distension and ultrasound features of polyhydramnios, hyperechoic bowel loops, honeycomb appearance of the bowel, and dilated bowel loops with normal peristalsis [10]. It can be misdiagnosed as Hirschsprung's disease, meconium ileus, anal atresia, and volvulus [11]. However, characteristic laboratory findings assist in diagnosis and limit unnecessary surgical interventions. The other genetic etiology for fecal chloride loss is microvillous inclusion disease. It is a rare autosomal recessive disorder that is characterized by severe watery diarrhea at birth. Diagnosis is established by colonoscopy and biopsy, which shows marked villous atrophy with electron microscopic evidence of intracellular microvillus inclusion bodies [12]. Moreover, severe cystic fibrosis and large villous adenomas (McKittrick-Wheelock syndrome) can present with severe, yet mucinous, diarrhea with subsequent severe volume contraction leading to metabolic alkalosis and low electrolytes similar to CCD [13] [14]. In such disorders, diarrhea is not at birth and diagnosis can be established by laboratory and radiological as well as colonoscopy. A final genetic etiology for diarrhea is congenital sodium diarrhea [15]. It is a rare disorder resulting from defective NHE (OMIM 270420). Its presentation is similar to CCD, yet with metabolic aci-

dosis and high fecal Na, not Cl. It is associated with high mortality and multiple congenital anomalies in 1/3 of patients. In CCD, the combination of persistent hypoK and metabolic alkalosis since birth may simulate Bartter's syndrome, yet in the latter syndrome urinary K is low and Cl is high and its hypoK, in CCD contrary to Bartter's syndrome, is easily corrected [16]. Early diagnosis and treatment, with adequate salt and K, are essential for normal growth and development and prevention of other severe complications. In oral replacement solutions, the initial dosage of electrolytes is Na 6 mmol/kg/day, K 6.5 mmol/kg/day, and Cl 12.5 mmol/kg/day in infants and less in older patients [6] [8]. The long-term chronic intrinsic renal disease complications of CCD have been attributed to three factors: a) recurrent severe volume contraction, b) dehydration-induced nephroangiosclerosis, and c) recurrent gouty arthritis with NSAID use with/without papillary necrosis. The first insult has been described in an epidemic of chronic kidney disease that emerged in Central America following heat dehydration due to activation of vasopressin and the aldose reductase-fructokinase pathway [17]. The second factor was chronic hypovolemic-induced nephrocalcinosis [18]. Virtually the majority of filtered Ca is absorbed passively in the paracellular route in proximal convoluted tubules and the ascending limb of Henle parallel to sodium. Only 10% is absorbed inversely to Na in the distal nephron [19]. Hence, with severe volume depletion, reabsorption of Ca is impaired, leading to urine supersaturation and crystal precipitation with papillary calcification and nephrocalcinosis. The last contributing factor was a maltreated gout with NSAIDs with/without recurrent papillary necrosis [20]. In our patient, the first factor was the most likely one. Regarding treatment of CCD, reduction of diarrhea has been described following oral butyrate, captopril, and proton pump inhibitors, yet subsequent studies had equivocal results [21]-[23]. Finally, recent gene therapy targeting SLC26A3 (Down Regulated in Adenoma, DRA) is promising and may provide dual benefits in correcting the diarrheal phenotype and improving gut barrier integrity and inflammation in pathogen infection or IBD [24].

4. Conclusion

CCD can be easily misdiagnosed. Serum and stool laboratory investigations and SLC26A3 genetic tests aid in diagnosis. Adequate lifelong sodium and potassium chloride oral replacement therapy is essential to avoid its serious complications.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Consent

Informed consent for publication of the case was obtained and is available upon request.

Author Contributions

Conceptualization & writing (original draft preparation): Kamel El-Reshaid and Shaikha Al-Bader. Patient follow up and data collection: Shaikha Al-Bader. Final draft preparation, review and editing: Kamel El-Reshaid. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest related to the contents of this article.

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