# Congenital chloride diarrhea misdiagnosed as pseudo-Bartter syndrome

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Congenital chloride diarrhea (CCD) is a rare autosomal recessive disease which is characterized by intractable diarrhea of infancy, failure to thrive, high fecal chloride, hypochloremia, hypokalemia, hyponatremia and metabolic alkalosis. In this case report, we present the first female and the second official case of CCD in Iran.

A 15-month-old girl referred to our hospital due to failure to thrive and poor feeding. She had normal kidneys, liver and spleen. Treating her with Shohl's solution, thiazide and zinc sulfate did not result in weight gain. Consequently, pseudo-Bartter syndrome was suspected, she was treated with intravenous (IV) therapy to which she responded dramatically. In addition, hypokalemia resolved quickly. Since this does not usually happen in patients with the pseudo-Bartter syndrome, stool tests were performed. Abnormal level of chloride in stool suggested CCD and she was thus treated with IV fluid replacement, Total parentral nutrition and high dose of oral omeprazole (3 mg/kg/day). She gained 1 kg of weight and is doing fine until present.

CCD is a rare hereditary cause of intractable diarrhea of infancy. It should be considered in infants with unknown severe electrolyte disturbances.

Key words: Congenital chloride diarrhea, hypochloremic and hypokalemic metabolic alkalosis, infants, pseudo-Bartter syndrome

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## **INTRODUCTION**

Congenital chloride diarrhea (CCD) is a rare autosomal recessive disease due to an intestinal absorption defect of chloride in exchange for carbonic acid (HCO<sub>2</sub>). This condition is more common in Finland, Poland, Kuwait and Saudi Arabia.<sup>[1]</sup> CCD belongs to the more common causes of severe congenital diarrhea, with prevalence in Finland of 1:20,000. It is caused by a defect of the SLC26A3 gene, which encodes a Na<sup>+</sup>-independent Cl<sup>-</sup>/  $HCO_{3}^{-}$  exchanger within the apical membrane of ileal and colonic epithelium. Founder mutations have been described in Finnish, Polish and Arab patients: V317del, I675-676ins and G187X, respectively. The Cl<sup>-</sup>/HCO<sub>2</sub><sup>-</sup> exchanger absorbs chloride originating from gastric acid and the cystic fibrosis transmembrane conductance regulator and secretes bicarbonate into the lumen, neutralizing the acidity of gastric secretion.<sup>[2]</sup>

Pseudo-Bartter's syndrome is a rare syndrome of electrolyte depletion, alkalosis and persistent failure to thrive. Hypokalemic metabolic alkalosis encounters in a variety of diseases as cystic fibrosis, hypertrophic pyloric stenosis and intestinal malrotation, treatment with purgatives or diuretics such as furosemide...; without renal tubular pathology, it will ultimately be corrected once the underlying disease is identified and treated. Any corrective fluid and electrolyte supplementation will therefore be a part of the basic disease treatment.

In this case-report, we present a complicated female case of CCD for the first time in Iran.

## **CASE REPORT**

A 15-month-old girl presented to our department (Al-zahra Hospital, Isfahan, Iran) for failure to thrive and poor feeding in 2011. She was born with polyhydramnios from healthy non-consanguineous parents at 32 weeks of gestation. She had a birth weight of 2050 g and body length of 42 cm, which were appropriate for her age. Following birth, she was admitted to the neonatal surgery department due to abdominal distention, lack of meconium and dilated bowel loops in abdominal X-rays and abdominal sonography (include figures), with suspection to intestinal obstruction and received conservative treatment. Hirschprung disease, hypertrophic stenosis of pylorus and intestinal obstructions were ruled out. She was discharged after 7 weeks with feeding tolerance and normal defecation. Serum levels of sodium (Na<sup>+</sup>), potassium (K<sup>+</sup>), blood urea nitrogen (BUN) and creatinine (Cr) at the time of discharge were 139 mEq/L (normal: 135-145),

Address for correspondence: Dr. Hossein Saneian, Department of Pediatrics, School of Medicine, Child growth and Development research center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: saneian@med.mui.ac.ir Received: 21-11-2012; Revised: 14-05-2013; Accepted: 29-08-2013 3.7 mEq/L (normal: 3.5-5.5), 19 mg/dL (normal: 6-20) and 0.9 mg/dL (normal: 0.3-1.2), respectively. In the abdominal ultrasonography, both kidneys had normal parenchymal echotexture without any stone or hydronephrosis. Liver and spleen were normal in size and echotexture. Intestinal loops were dilated.

After 2 months, she was admitted to a hospital because of moderate dehydration suspecting polyuria. Serum levels of Na<sup>+</sup>, K<sup>+</sup>, BUN and Cr were 110 mEq/L, 2.7 mEq/L, 40 mg/dL and 0.5 mg/dL, respectively. Urine analysis was normal with a pH of 6. After 5 days, she was discharged in a stable condition. However, she was presented to another hospital due to poor feeding and anuria after 10 days. Regarding her past medical history, she was referred again to our center for specific workup.

At the time of admission, physical examination showed severe dehydration, severe failure to thrive without organomegaly and low grade fever with mild diarrhea. Laboratory data revealed white blood cell count, hemoglobin, platelets, serum Na<sup>+</sup>, serum K<sup>+</sup>, BUN and Cr, 5800/mm<sup>3</sup>, 10.6 g/dL, 880 × 10<sup>3</sup>/mm<sup>3</sup>, 133 mEq/L, 2.6 mEq/L, 130 mg/dL and 5.1 mg/dL, respectively. Blood gas analysis showed a normal anion gap acidosis with a pH of 6.9, carbon dioxide partial pressure (pCO<sub>2</sub>) of 10 mmHg and HCO3<sup>-</sup> of 4 mEq/L (normal: 22-26). The enzymes alanine aminotransferase and aspartate aminotransferase, as liver function indicators, were normal. Finally, she underwent peritoneal dialysis. After 4 days, Cr level decreased to 1.1. Shohl's solution (polycitra) was then prescribed for her. Distal renal tubular acidosis (type I) was considered as the main diagnosis and she was discharged home in a stable condition.

While being treated with Shohl's solution, thiazide and zinc sulfate, the patient was followed-up for 6 months in the nephrology clinic. She did not gain weight within this period and returned with severe dehydration. She was resuscitated with 40 cc/kg normal saline. New laboratory findings showed a serum Na<sup>+</sup> level of 134 mEq/L, K<sup>+</sup> level of 2.1 mEq/L and chloride (Cl<sup>-</sup>) level of 82 mEq/L (normal: 98-108). Metabolic alkalosis (pH = 7.57, pCO<sub>2</sub> = 32 mmHg and  $HCO_3^- = 34 \text{ mEq/L}$ ) and hyperreninemia (129  $\mu$ IU/ml) and hyperaldosteronemia (317 pg/ml) was also observed. At this point, pseudo-Bartter syndrome was suspected and the treatment began promptly. She had a dramatic response to intravenous (IV) therapy and hypokalemia resolved quickly (despite what is normally seen in pseudo-Bartter syndrome), urine electrolytes on admission were: Na<sup>+</sup> 67 mEq/L, K<sup>+</sup> 28.3 mEq/L and Cl<sup>-</sup> 2 mEq/L. Consequently, all treatments were halted and a new diagnostic workup was planned to reach the definite diagnosis. A new history from the mother revealed that the patient has had loose defecation during the past months which has been considered as normal by the mother and she had never passed normal stools; watery content of diarrhea since infancy had been confused with that of urine.

Following consultation with our gastroenterologist, measuring stool electrolytes showed Na<sup>+</sup> of 64 mEq/L (normal: 20-30 mEq/L), K<sup>+</sup> of 50 mEq/L (normal: 55-65 mEq/L) and Cl<sup>-</sup> of 120 mEq/L (normal: 5-20 mEq/L) were confirmed with repeated analyses. Stool pH was 5. Upper gastrointestinal endoscop, rectosigmoidoscopy, histopathology of duodenoum and rectosigmoid were normal. Stool microscopy and cultures were normal. Stool reductant material and fat were negative. Celiac serologic tests were negative. Cystic fibrosis was ruled out by normal sweat test. With these findings, CCD was established for her and treatment began by IV fluid replacement and total parentral nutrition, which resulted in a 1-kg weight gain after 1 month. Fortunately, the patient was discharged after 1 month with oral omeprazole, 3 mg/kg/day, potassium chloride (KCl 2 mEq/kg/day), sodium chloride (NaCl 3 mEq/kg/day), cholestyramine (150 mg/kg/day), multivitamin (as recommended daily allowance [RDA]) and mineral pills (as RDA). She was followed with gastroenterological, nutritional and nephrological services for 1 year. Her condition gradually improved and she does not have a major problem except mild to moderate delayed growth and development at the present time. Her food tolerance is also acceptable.

### DISCUSSION

Although CCD is lethal if untreated, early diagnosis and aggressive fluid and electrolyte replacement therapy in infancy can improve the survival of patients. CCD manifests prenatally with watery diarrhea, which leads to polyhydramnios and often premature birth.[3,4] Newborns with CCD have abdominal distention and absence of meconium which may be mistaken for intestinal obstruction and watery diarrhea with urine.[1,5-7] Undiagnosed and thereby untreated children die very soon from severe dehydration due to continuous loss of fluid and electrolytes in the stool. Effective treatment is mostly symptomatic and includes daily replacement therapy with NaCl, KCl and water. Lifelong replacement of fluid and electrolytes may result in normal growth and development and a favorable long-term outcome.[8,9] Recently, proton pump inhibitors have also been shown to be helpful in the treatment of patients with CCD.<sup>[10]</sup> Butyrate is a choice but was not accessible in Iran;<sup>[11]</sup> so patient was treated by high-dose omeprazole.<sup>[11]</sup>

Several different disorders, including Bartter syndrome, are generally mistaken for CCD. In both disorders, dehydration, hypochloremic metabolic alkalosis, hypokalemia and high renin, angiotensin and aldosterone levels are seen. Defects in CCD are located in intestinal Cl<sup>-</sup>/HCO3<sup>-</sup> exchangers, but in Bartter syndrome, it is located in renal Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> transporters. Unlike high urinary Cl<sup>-</sup> concentration in Bartter syndrome, low urinary and high fecal Cl<sup>-</sup> are observed in CCD.<sup>[6]</sup>

Polyuria is the main symptom of Bartter syndrome, while the main symptom in CCD is diarrhea. In our case, the defecation was not normal, but it was misdiagnosed by her mother and physicians with polyuria.

They thought that a mild loose defecation is normal stool of breastfed infants. The partially treatment of this case in between several hospital admission periods was due to the order of physicians, which advised the mother to compensate the volume loss by oral and occasionally, IV hydration.

It is mentioned that the patients without appropriate diagnosis, die soon.<sup>[7]</sup> In the reported case, the reason of surveillance despite delayed diagnosis may be the alertness of her mother, high economic status of her family and their serious follow-up.

In brief, CCD is a rare hereditary disease in very young children and is considered as a diagnosis of exclusion. It should be considered in children with failure to thrive, diarrhea and electrolyte disturbances who do not respond to conservative or specific treatments through time.

CCD is one of the most causes of intractable diarrhea of infancy; and considering its high incidence in our neighbor Arab countries,<sup>[12]</sup> it should be more prevalent in Iran. It seems that the disease is un- or misdiagnosed in Iran and this is the reason why only two cases are reported until now.

It is strongly advised to pediatricians to have the CCD in their minds as a common cause of intractable diarrhea infancy. We hope more cases be diagnosed and treated in future years by Iranian pediatricians.

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