Type IV neonatal Bartter syndrome complicated with congenital chloride diarrhea

Hale Sakallı[1], Hakan İbrahim Bucak[2]

[1] Department of Pediatric Nephrology, Numune Teaching and Research Hospital, Adana, Turkey
[2] Departments of Pediatrics, Numune Teaching and Research Hopital, Adana, Turkey

Summary

Background: Pseudo-Bartter syndrome encompasses a heterogenous group of disorders similar to Bartter syndrome. Sometimes a few status may be nested, as in our case presented here.

Case Report: An 8-month-old boy was referred to our hospital with of intractable diarrhea, polyuria, persistent hypokalemia, abdominal distension and failure to thrive. He was born in the 34 6/7 gestational week (GW) to consanguineous parents. In the 30th GW polyhydramnios was verified by ultrasonography. The laboratory results showed hypokalemic-hypochloremic metabolic alkalosis, hyponatremia, and increased urinary loss of chloride, potassium and calcium. An audiogram test revealed complete sensorineural deafness. Ultrasonography revealed medullary nephrocalcinosis in both kidneys. Elevated plasma renin activity and aldosterone were found and a provisional diagnosis of type-IV neonatal Bartter syndrome was made. Treatment with indomethacin, spironolactone and additional intake of NaCl/KCl was initiated. Despite these therapies, the child's diarrhea persisted but serum potassium concentration normalized, and hypercalciuria and urine output reduced. After determining the high fecal chloride concentration, there was an immediate decompensation of the disease on indomethacin withdrawal, thus a diagnosis of type IV neonatal Bartter syndrome complicated with congenital chloride diarrhea was considered. Indomethacin, spironolactone and supplementary therapies with NaCl/KCl were continued, which resulted in the normalization of serum electrolytes as well as his physical development, but high contents of chloride in urine and faeces and nephrocalcinosis remains unchanged during 1-year follow-up.

Conclusions: Because of the clinical and laboratory simulations between the various diseases that lead to hypokalemic-hypochloremic metabolic alkalosis, patients must be evaluated carefully.

key words: Bartter syndrome • congenital chloride diarrhea

Author's address: Hale Sakallı, Pediatric Nephrologist, Baskent University Faculty of Medicine Department of Pediatric Nephrology, Konya, Turkey, e-mail: hales1972@yahoo.com

BACKGROUND

Congenital chloride diarrhea (CLD) is the most frequent secretory-type diarrhea during the infantile period in the presence of normal intestinal mucosa. The disease is an autosomal recessive disorder of intestinal Cl/HCO3 exchange caused by mutations in the SCL26A3 gene and characterized by persistent Cl-rich diarrhea leading to hypochloremic-hypokalemic metabolic alkalosis from birth. Treatment is symptomatic, and replacement therapy with NaCl and KCl has been shown to be effective in children, but the long-term prognosis remains unclear. Although approximately half of the reported cases to date are from Finland, a much higher incidence has been reported among Arabic people. Bartter syndrome, cystic fibrosis and pyloric stenosis also lead to similar electrolyte disturbances in the early neonatal period. The diagnosis of CLD can be confirmed by measuring the fecal concentration of Cl, which always exceeds 90 mmol/L in patients with normal water and electrolyte balance [1–3].

Batter syndrome is an autosomal recessive inherited renal tubular disorder characterized by hypokalemic-hypochloremic metabolic alkalosis, hyperreninemia, hyper-prostaglandinism, normal blood pressure, with increased urinary loss of sodium, chloride, potassium, calcium and prostaglandins [4–6]. The onset may be during the neonatal period, infancy or childhood. It consists of a rare tubulopathy, which can manifest with varied phenotypes and is easily confused with more common conditions [4]. This report describes a case of type IV neonatal Batter syndrome with sensorineural deafness complicated with CLD.

CASE REPORT

An 8-month-old boy was referred and admitted to our hospital with intractable diarrhea, polyuria, persistent hypokalemia, abdominal distension and failure to thrive. Potassium supplement was commenced, but led to very little improvement of the symptoms. The patient's family history was notable for an elderly sibling who had died due to similar clinical features. His history that was taken from his parents was: he had been born to consanguineous parents, his weight was 1800 gr at 34 6/7 wk of gestational age and he was delivered by caesarean section because of fetal distress. Apgar score was 9 at 5 min. Maternal polyhydramnios had been present through the 30th week of gestation. After birth he had exchange transfusion and phototherapy because of hyperbilirubinemia on the 2nd to 6th days of his life. Then he developed non-bilious vomiting, frequent diarrhea episodes, abdominal distension and failure to thrive. His parents had noticed that their son had hearing loss and polyuria. At 6 months of age, an incarcerated inguinal hernia was diagnosed and repaired at a hospital. There was no history of administration of aminoglycosides.

On examination the child weighed 4.1 kg, length was 60 cm and head circumference was 38 cm, all of which were below the 3th percentile for the age. He was dehydrated and his facial dysmorphism was significant, with triangularly shaped face, prominent forehead, large eyes, protruding ears and drooping mouth. He was normotensive and had no localizing sings on neurological examination. Investigations showed hypokalemic-hypochloremic metabolic alkalosis (serum potassium 2.3 mEq/L; chloride 85 mEq/L; bicarbonate 40 mEq/L; pH 7.52; and PCO$_2$ 44 mm), as well as hyponatremia (129 mEq/L), normal serum levels of creatinine, albumin, calcium and magnesium, with urine revealing hyposthenuria (specific gravity 1007) and increased urinary loss of chloride, potassium and calcium (chloride 68 mEq/L; potassium 49 mEq/L; calcium to creatinine ratio: 0.49). Urine output was 8 mL/kg/hr. An audiogram test revealed complete sensorineural deafness (hearing threshold levels were all above 115 dB for the frequencies of 500–4000 Hz). Ultrasonography of the abdomen revealed significant features of medullary nephrocalcinosis in both the kidneys. Elevated plasma renin activity (57 ng/ml/hr, normal range: 2.4–37 ng/ml/hr) and aldosterone (1400 pg/ml, normal range: 20–760 pg/ml) were found and a provisional diagnosis of type IV neonatal Bartter syndrome was made. Indomethacin treatment was initiated at a dose of 1 mg/kg per day and the child was maintained on supportive care, potassium supplements and dietary advice. Despite these therapies the child's diarrhea persisted and urine output reduced to 6 mL/kg/hr. Blood values at the first week of hospitalization were sodium 131 mEq/L; potassium 2.7 mEq/L; chloride 91 mEq/L; bicarbonate 33 mEq/L; pH 7.47; and PCO$_2$ 40 mm. The dose of indomethacin was increased to 2 mg/kg/day and combined with spironolactone (2 mg/kg/day). He continued to have watery stools 6–8 times per day, but serum potassium concentration normalized, hypercalciuria reduced (calcium to creatinine ratio: 0.35) and urine output declined to 3 ml/kg/hr. He was discharged at on the 16th day of hospitalization. Ten days later the patient was readmitted with watery diarrhea (12–15 times per day), dehydration, and abdominal distension. Laboratory investigations again revealed hypokalemic-hypochloremic metabolic alkalosis. Microbiologic evaluation of the stool revealed no bacterial or parasitic infectious agents. Stool pH was 5, microscopic examination with Sudan red stain showed no fat droplets, and measurement of carbohydrate using the Clinitest reagent for reducing substances was negative. The breath hydrogen test was also normal. Fecal chloride concentration was 152 mmol/L, sodium 84 mmol/L, and potassium 32 mmol/L, fulfilling the 2 diagnostic criteria of CLD (fecal chloride content >90 mmol/L and fecal cationic gap F-Na$^+$ + K$^+$ < Cl$^-$). The sweat test indicated 52 mEq/L of chloride. A missed diagnosis was made as CLD. There was an immediate decompensation of the disease on indomethacin withdrawal, therefore a diagnosis of type IV neonatal Bartter syndrome complicated with CLD was made. In addition to previous medicines, supplementary therapy was initiated with a dose of 6 mmol/kg chloride per day, divided equally between NaCl and KCl. A trial of omeprazole (10 mg/day) had no effect on stool frequency. He recovered and returned home on the 20th day of the second hospitalization. He had been passing watery stools 4–6 times per day, but medications resulted in a significant reduction in urine volume and hypercalciuria, and correction of biochemical abnormalities. During follow-up he required frequent hospitalizations because of recurrent episodes of diarrhea, but growth and development are satisfactory after 16 month of treatment, with height being 70 cm, and weight 7.7 kg, which are still below the 3th percentile for age. His serum electrolyte concentrations and kidney function are normal, but he continues to excrete chloride in urine and feces, and nephrocalcinosis remains unchanged (Figures 1 and 2, taken after 16 month of treatment).

Figure 1. Photography of the patient taken after 16 month of treatment. Facial dysmorphism and abdominal distension is significant.

Figure 2. Photography of the patient taken after 16 month of treatment. His growth and development are satisfactory after 16 month of treatment.

DISCUSSION

Congenital chloride diarrhea is an autosomal recessive disorder of intestinal electrolyte absorption. It is characterized by persistent secretory diarrhea resulting in polyhydramnios and prematurity prenatally, and dehydration, hypoelectrolytemia, hyperbilirubinemia, abdominal distention, and failure to thrive immediately after birth [2,3,7]. It is caused by mutations in a plasma membrane protein, the solute-linked carrier family 26 member A3 (SLC26A3) protein, which encodes for an epithelial anion exchanger for Cl- and HCO3-. The main clinical symptom is a lifetime watery diarrhea with a high Cl- content and low pH, causing dehydration and hypochloremic-hypokalemic metabolic alkalosis. CLD may be fatal if not adequately treated by substitution of NaCl, KCl and fluid lost in the feces. Long-term prognosis is generally favorable, but complications such as renal disease, inflammatory bowel disease, hyperuricemia, inguinal hernias, spermatoceles and male subfertility are possible [2,3,7].

Bartter syndrome comprises several closely related renal tubular disorders that can be grouped into at least 3 clinical phenotypes: infantile (neonatal) variant of Bartter syndrome, classic Bartter syndrome, and Gitelman syndrome [4,5].

Neonatal Bartter syndrome is observed in newborn infants and characterized by polyhydramnios, premature delivery, life-threatening episodes of fever, polyuria, severe electrolyte derangements and dehydration during the early weeks of life, growth retardation, hypercalciuria, and early-onset of nephrocalcinosis. Other clinical features are characteristic facies with thin, triangular face, prominent forehead, large eyes, protruding ears, drooping mouth, strabismus, convulsions and increased susceptibility to infections [4,5]. Recently, a clinically distinct group of patients with neonatal Bartter syndrome with sensorineural deafness has been recognized among those with neonatal Bartter syndrome (type IV) [8,9]. "Classic" Bartter syndrome is mostly observed during infancy and early childhood and is characterized clinically by polyuria and growth retardation. Nephrocalcinosis is typically absent despite hypercalciuria. The hypocalciuric, hypomagnesemic variant of Bartter syndrome (Gitelman syndrome), is observed in older children and early adulthood, presenting with predominantly musculoskeletal symptoms [4,5].

Clinical features of our patient – facial dysmorphism, failure to thrive, gastroenteritis, polyuria, dehydration, hyponatremia, hypokalemic-hypochloremic metabolic alkalosis, hyperreninemia, hyperaldosteronism, hypercalciuria accompanied by early-onset of nephrocalcinosis, sensorineural deafness and absence of hypomagnesemia – led us to make a provisional diagnosis of type IV neonatal Bartter syndrome. His response to the therapy (potassium supplements and indomethacin plus spironolactone) was satisfactory, resulted in a significant reduction in urine volume and hypercalciuria, but frequency of diarrhea episodes remains unchanged. Further investigations are needed to explain the cause of the intractable diarrhea and high level of chloride found in the feces and sweat.

In chloride diarrhea, juxtaglomerular hyperplasia, hyperreninemia and hyperaldosteronism, leading to hypercalciuria and hypokalemia, simulate Bartter syndrome. As in the latter disorder, inhibitors of prostaglandin synthetase have beneficial effects, as in our patient [10]. In patients with CLD, although treatment with NaCl and KCl offers protection from renal involvement in childhood, the long-term renal outcome remains unclear and the main feature of the renal injury reported by Wedenoja et al. was nephrocalcinosis, without hypercalciuria or nephrolithiasis with small kidneys and commensurately reduced glomerular filtration rates [3].

The patient's clinical features, including the history of antenatal polyhydramnios and preterm delivery, early-onset of nephrocalcinosis with hypercalciuria, presence of sensorineural deafness and beneficial effects of indomethacin, were compatible with the clinical aspects of neonatal Bartter syndrome. Unusual features were the presence of hyperbilirubinemia, inguinal hernia, intractable watery diarrhea episodes and high chloride content of the feces and the sweat, which are more peculiar to CLD. On the other hand, a literature search revealed that a female case of CLD was reported by Höglund et al, whose physical status and laboratory tests were normal except for mild high-frequency sensorineural hearing loss [11]. Because of this, we were unable to distinguish the exact etiology of sensorineural hearing loss in this patient. It would be better if we could have confirmed both of the diagnoses by identifying the related genes, but it was impossible because of the mismatch of the family.

In patients with CLD, the oral intake of chloride, sodium and potassium must exceed fecal output (ie, there must be a positive gastrointestinal balance) so that obligatory losses in sweat can be replaced. A positive balance can best be ensured by a high intake of chloride, even though it exacerbates diarrhea. Aichbichler et al. concluded that suppression of gastric chloride secretion by a proton-pump inhibitor, omeprazole reduces fecal electrolyte losses in patients with this disorder and thus promotes a positive gastrointestinal balance [12]. However, this treatment does not reduce the need for careful monitoring of dietary intake, serum electrolyte concentrations, and urinary chloride excretion, as in our patient.

Conclusions

We reported an interesting childhood case of type IV neonatal Batter syndrome complicated with CLD. According to results of our literature search, this case represents the first documented case of type IV neonatal Bartter syndrome complicated with CLD. Because of the similarities between the 2 diseases, evaluation of the patients must be done carefully, and screening of fecal chloride concentration and hearing test should be performed in all patients, especially infants with a family history of an undefined intestinal absorption defect with a clinical picture including polyhydramnios, prematurity, nephrocalcinosis and chronic watery diarrhea.

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