CASE REPORT

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Congenital chloride diarrhea misdiagnosed as Bartter syndrome

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Congenital chloride diarrhea is the most frequent secretory-type diarrhea during the infantile period in the presence of normal intestinal mucosa. The disease has an autosomal recessive inheritance. Although approximately half of the reported cases to date are from Finland, a much higher incidence has been reported among Arabic people. The defective gene is SLC26A3, which encodes a Na–independent CL/HCO3 exchanger that is expressed primarily in the apical brush border membrane of ileal enterocytes and colonic epithelium. The disease is characterized by dehydration and hypochloremic metabolic alkalosis. Bartter syndrome, cystic fibrosis and pyloric stenosis also lead to similar electrolyte disturbances in the early neonatal period. The diagnosis of congenital chloride diarrhea can be confirmed by measuring the fecal concentration of Cl, which always exceeds 90 mmol/L in patients with normal water and electrolyte balance. Here, we report a patient with congenital chloride diarrhea misdiagnosed as Bartter syndrome until 20 months of age.

Key words: Chloride diarrhea, infant, Bartter syndrome

Bartter sendromu tanısıyla izlenen bir konjenital klor kaybettiren ishal olgusu

Konjenital klor kaybettiren ishal, infantil dönemde normal intestinal mukoza varlığında en sık rastlanan sekretuar tip ishal sebebidir. Hastalığın otozomal resesif kalıtımı vardır. Şimdiye kadar rapor edilen olguların yaklaşık yarısı Finlandiya'dan rapor edilmekle birlikte, Arabik toplumda daha yüksek bir sıklık bildirilmiştir. Defektif gen olan SLC26A3, primer olarak ileal enterositlerin apikal fırçamsı kenar membranından ve kolon epitelinden dışarıya çıkan Na bağımsız CL/HCO3 değiştiriciyi kodlamaktadır. Hastalık, dehidratasyon ve hipokloremik metabolik alkaloz ile karakterizedir. Bartter sendromu, kistik fibrozis ve pilor stenozu da erken neonatal dönemde benzer elektrolit bozukluklarına yol açarlar. Klor kaybettiren ishalin tanısı fekal Cl konsantrasyonunun ölçülmesiyle doğrulanır ki normal su ve elekrolit balansı olan hastalarda gaitada CL değerinin 90 mmol/L'yi aşması ile tanı alır. Burada, 20 aylık olana dek Bartter sendromu olarak tanı alan bir klor kaybettiren ishal olgusu takdim edilmektedir.

Anahtar kelimeler: Klor kaybettiren ishal, infant, Bartter sendromu

INTRODUCTION

Congenital chloride diarrhea (CLD) (OMIM #214700) is a rare autosomal recessive disease with chronic secretory diarrhea. One-fifth of the 250 cases reported worldwide originate from Finland, where incidence is around 1:30,000 to 1:40,000. Much higher local incidences of even 1:3,200 to 1:5,000 appear among Arabic people due to consanguineous marriages (1). The defective gene in CLD, the solute carrier family 26 member 3 (*SLC26A3* alias *DRA*), encodes a Cl^-/HCO_3^- exchanger expressed primarily on the apical brush border of the ileal and colonic epithelium (2,3). CLD is characterized by profuse Cl^--rich diarrhea leading to dehydration and hypochloremic and hypokalemic metabolic alkalosis soon after birth (4). CLD diagnosis is based on its typical clinical picture and a high concentration of fecal Cl^-, ex-

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ceeding 90 mmol/L after correction of the fluid and electrolyte depletion. While salt substitution with NaCl and KCl allows a favorable outcome, untreated CLD is usually lethal even during the first weeks or months of life (5). The differential diagnosis of CLD includes other inherited diarrheas, and CLD is sometimes confused with diseases showing at least partly similar electrolyte disturbances in the early neonatal period (4).

CASE REPORT

A 20-month-old boy followed for Bartter syndrome in another center presented to our department due to watery diarrhea for the last two months. His medical data revealed parental consanguinity and a history of polyhydramnios, premature birth and a three-month period with incubator plus ventilator and umbilical vein catheterization. After neonatal intensive care, the patient had been hospitalized five times due to moderate to severe dehydration. The diagnosis of Bartter syndrome had been established based on electrolytes (Cl: 89 mEq/L, K: 2.4 mEq/L), blood gas analysis (HCO_3^-: 28 mmol/L or pH: 7.5), hyperreninemia (128 µIU/ml), and hyperaldosteronemia (315 pg/ml) at the local hospital. The treatment involved amiloride plus hydrochlorothiazide (6.5 mg/day) and chloride replacement with KCl ampules (10 mEq/day). At the time of admission to our department, his body weight was 8400 g (<3 p), height 80 cm (25-50 p), head circumference 46 cm (3 p), pulse rate 132/min, respiratory rate 32/min, and blood pressure 90/60 mmHg. He had moderate dehydration and diaper dermatitis. Laboratory analysis revealed hypochloremia (plasma Cl^- 85 mEq/L), hypokalemia (plasma K^+ 2.6 mEq/L) and metabolic alkalosis (vein blood HCO_3^- 27). Liver and kidney functions were normal and serum chloride level remained low, at 88-90 mEq/L, during the follow-up period. Urine electrolytes on admission were: Na^+ 70 mEq/L, K^+ 27.3 mEq/L, and Cl^- <20 mEq/L. After intravenous fluid and electrolyte resuscitation, urine Cl^- level was <10 mEq/L. Plasma renin activity was 304 µIU/ml (normal reference: 2.8 to 39.9) and aldosterone was 752 pg/ml (normal reference: 29.4 to 161.5). Abdominal ultrasonography and stool microscopy and pH were normal. Stool cultures, reductant material and fat were negative. Celiac serology remained negative. Cystic fibrosis was ruled out by normal sweat test. During hospitalization, watery diarrhea was continuous. Samples for measuring stool electrolytes had failed many times, and the specimen was eventually taken with a nasogastric tube aspiration from the rectum. The results showing Na^+ of 85 mEq/L, K^+ of 50 mEq/L and Cl^- of 154 mEq/L were confirmed with repeated analyses. Later, genetic analysis for SLC26A3 mutations (University of Helsinki, Finland) revealed that the patient had the homozygous Arabic founder mutation c.559G>T (p.G187X) for CLD (1). Medical treatment options of lansoprazole, cholestyramine and butyrate complex were also given, respectively, but all of them failed. The patient has been receiving oral substitution with NaCl and KCl and is being followed as an outpatient.

DISCUSSION

In 1945, Darrow and Gamble (6,7) described the first cases of CLD under the name of congenital alkalosis with diarrhea. Later, familial enrichment of the cases proved the autosomal recessive inheritance of the disease, which was called congenital chloride diarrhea (CLD) (8). The onset of CLD is intrauterine, leading to polyhydramnios. Even at the end of the second trimester, ultrasonic investigation of a fetus with CLD reveals dilated intestinal loops, resulting in suspicion of the disease (9). The birth is generally at least two weeks premature, and the lack of meconium (these patients do not have meconium due to congenital abundant watery diarrhea), abdominal distention and watery diarrhea are hallmarks of CLD (4). As the disease is rare, however, misdiagnoses are possible. First, watery diarrhea may be easily confused with urine. Soon after, chronic dehydration reduces the amount of diarrhea, making diagnosis of untreated CLD even more difficult (5). Our patient had been diagnosed as Bartter syndrome in a local hospital. He had a history of recurrent dehydration, hypochloremic metabolic alkalosis, and high renin, angiotensin and aldosterone levels. Before admittance to our center, his chronic diarrhea had been reported to continue for the last two months only. However, the detailed history revealed that he had never passed normal stools. The watery content of diarrhea since infancy had been confused with that of urine, and fecal samples had been difficult to obtain. In our patient, hypochloremic and hypokalemic metabolic alkalosis had led to the diagnosis of Bartter syndrome (OMIM #241200). As both CLD and Bartter syndrome are associated with hypokalemic metabolic alkalosis, each of these two diseases should be kept in mind in the differential diagnostics of the other. The si-

tes of the basic defect, intestinal Cl^-/HCO_3^- exchange defect in CLD and renal Na^+-K^+-$2Cl^-$ transporter defect in Bartter syndrome (11), are different. Therefore, Cl^- is lost into stools in CLD and into the urine in Bartter syndrome, making differential diagnostics possible independent of similar hypokalemic metabolic alkalosis. While Bartter syndrome involves increased urinary Cl^-, both the severe dehydration and intestinal loss of Cl^- in untreated CLD make the urine Cl^--free. Therefore, differences in renal excretion of Cl^- in these two disorders are evident. After performing urine Cl^- measurement, the study of fecal electrolytes is needed to confirm the diagnosis of CLD. It is also worth remembering that fecal Cl^- may be low, even 40 mmol/L, in untreated CLD associated with severe dehydration (11). The history of "no diarrhea" in our case was thus based on severe dehydration. After suspicion of CLD, rectal stool aspiration with a nasogastric tube and study of stool electrolytes in repeated samples led to the diagnosis. Although the clinical picture and high fecal Cl^- are the basis for the diagnosis in CLD, searching for disease-causing *SLC26A3* mutations is possible. Thus far, over 30 mutations have been reported to cause CLD, with no evidence of genotype-phenotype correlation (12). Therefore, independent of mutation, the clinical picture of CLD seems to be highly similar. In our case, finding the Arabic founder mutation for CLD was a highly expected result based on the uneven geographical distribution of the disease (1).

In conclusion, in patients with hypochloremic and hypokalemic metabolic alkalosis, in addition to a detailed medical history including prenatal and early postnatal findings, synchronous serum, urine and stool chloride measurements are essential. As seen in our case, rectal aspiration of stools with a nasogastric tube may help in obtaining fecal sample, and if needed, analysis of the mutation responsible for CLD is possible to confirm an uncertain diagnosis. As the local incidences of CLD may be as high as even 1:3,200 among Arabic people (1), CLD is worth remembering in the differential diagnostics in children with a tendency to chronic dehydration, failure to thrive, slow growth, and hypokalemic and hypochloremic metabolic alkalosis. Although salt substitution with NaCl and KCl has no effect on the chronic diarrhea, it allows the maintenance of normal electrolyte and acid-base balance, normal growth and development, and favorable outcome of the disease (5).

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