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Surgical consequences in infants with delayed diagnosis of congenital chloride diarrhea

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ABSTRACT

Despite the usual typical presentation, congenital chloride diarrhea (CCD) poses multiple diagnostic challenges. It has an incidence of 1/5000 in Saudi Arabia. CCD can mimic intestinal obstruction and result in avoidable surgical interventions. Contributing factors are abdominal distension and the watery (urine-like) diarrhea that is often interpreted as delayed passage of meconium. Surgical interventions would unnecessarily increase the morbidity. Therefore, a high index of suspicion and educating neonatologists, general pediatricians, and pediatric surgeons regarding this diagnostic entity is essential. Here we describe five such cases.

Keywords: Diarrhea, congenital chloride diarrhea, intestinal obstruction

Case Report

INTRODUCTION

Congenital chloride diarrhea (CCD) is a rare disorder with multiple diagnostic challenges. More than one-half of patients are found in Finland, Poland, and the Arab countries (1). Its incidence in Saudi Arabia is 1/5000, while in Kuwait is 1/3200 (2,3). SLC26A3 gene encodes chloride/bicarbonate exchange transporter in the gut. When detected, CCD results in severe watery diarrhea and the rennin-angiotensin system is activated leading to hypochloremia, hyponatremia, hypokalemia, and metabolic alkalosis (1). Moreover, CCD patients typically present with high fecal chloride (higher than the sum of fecal potassium and sodium) (4). Chloride-free urine is another associated finding (2,4). Consequently, chronic dehydration, chronic kidney disease, and even death may follow if not recognized early. Multiple misdiagnoses, such as Bartter syndrome, Hirschsprung disease (HD), and small intestinal obstruction (IO), were reported (1,5,6).

We hypothesize that a delayed CCD recognition can result in catastrophic consequences, both for the patient and the health system. We aim at listing CCD as a possible differential diagnosis in neonates resembling IO. This may help reducing the morbidity and mortality.

CASE PRESENTATIONS

Here, we report 5 infants with a delayed diagnosis of CCD. We obtained their information through a retrospective file review after obtaining approval from local ethical committee. No informed consent was required. They all underwent laparotomy for suspected IO.

CASE 1

A female infant was born through Cesarean delivery (CD) at 33 weeks of gestation (birth weight (BW), 1.41 kg) due to polyhydramnios and premature rupture of membranes. No antenatal ultrasound (AUS) findings were documented. Postnatally, she developed abdominal distension (AD) and visible bowel loops (VBL) and did not pass stool for 3 days, suggesting IO secondary to HD. After 5 days of birth, she underwent laparoscopy and colostomy formation and colonic biopsies were taken. They showed ganglion cells. Subsequently, her colostomy was closed at 41 days.

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The patient continued to have failure to thrive and hypoactivity requiring parenteral nutrition (PN). When 5 months old (weight, 2.4 kg), diarrhea was recognized for the first time, her serum potassium was 2.6 mmol/L; sodium, 131 mmol/L; chloride, 73 mmol/L; and CO_2, 40 mmol/L. No stool electrolyte (SE) measurements were performed. However, gene testing confirmed CCD, i.e., a homozygous disease causing sequence variants (c.559G>T) of nonsense mutation (p.G187X) in the exon 5 of the SLC26A3 gene.

Appropriate fluid management and salt supplements were initiated. The patient's weight, activity, and alertness improved.

CASE 2

A female infant was born at 33 weeks gestation by spontaneous vaginal delivery (SVD) with a BW of 2.1 kg. AUS showed dilated bowel loops (DBL). When 1 week old, she had AD and VBL and delayed passage of stool. Abdominal X-ray and ultrasound suggested HD, but barium enema showed no evidence of obstruction. Furthermore, full thickness rectal biopsy on the eighth day confirmed the presence of ganglion cells.

The patient continued to have intermittent AD, suggestive of chronic intestinal pseudo-obstruction. At 3 months of age, a repeated contrast enema was suspicious for a volvulus. Diagnostic laparotomy showed intestinal malrotation and Ladd's procedure was performed.

At 8 months of age, she presented again with AD and watery diarrhea. Her investigations revealed potassium, <2.4 mmol/L; sodium, 135 mmol/L; chloride, < 82 mmol/L; and CO_2, >41 mmol/L. SE were not measured due to its collection failure. However, the patient was started on salt supplements and did well thereafter.

Confirmatory genetic study was positive at the age of 3 years, i.e., homozygous for disease causing sequence variants of the nonsense mutation c.559G>T;p.G187X in the exon 5 of the SLC26A3 gene.

CASE 3

A male infant was born at 37 weeks gestation (BW, 2 kg) by elective CD due to polyhydramnios. AUS showed AD and DBL. At birth, VBL and excessive watery diarrhea were noted. His initial laboratory tests showed an arterial pH of 7.45 and normal electrolytes. Plain abdominal X-ray showed DBL with excessive gaseous distension. Barium meal and follow-up revealed severe DBL with slow transit time. Thus, IO was suspected and the patient underwent laparotomy. However, there was no evidence of mechanical obstruction.

He continued not to tolerate oral feeds and therefore required PN. His SE was showed chloride, 149 mmol/L; sodium, 134 mmol/L; and potassium, 5.5 mmol/L. Genetic testing at the age of 4 years was positive for homozygous mutation (G187X) at the c.559G>T sequence variant in the SLC26A3 gene. (amino acid change G187X).

Currently, at 10 years, the patient is on salt supplements and has a normal growth rate and development.

CASE 4

A female infant, who had a sibling with CCD, was born at 35 weeks gestation (BW, 2.2 kg) through SVD. Her AUS showed polyhydramnios. After birth, the girl had mild AD with VBL and watery diarrhea. Her blood pH was 7.4; sodium, 137 mmol/L; potassium, 4.7 mmol/L; and chloride, 102 mmol/L. SE showed chloride, 83 mmol/L; potassium, 12.6 mmol/L; and sodium, 142 mmol/L.

Parenteral nutrition was initiated due to repeated failures of oral feedings resulting in AD. Oral salt supplements were introduced to control frequent electrolyte disturbances, resulting in clinical and biochemical improvement. By 6 weeks of age, the family stopped oral supplements. One month later, AD recurred and IO was diagnosed. Therefore, the patient underwent laparotomy with resection of 25 cm of the terminal ileum (no further details were found). After 3 months, the patient presented again with diarrhea. Serum sodium was 130 mmol/L; potassium, 3 mmol/L; and chloride, 89 mmol/L, with a venous pH of 7.71. Her SE showed chloride of 113 mmol/L; sodium, 42 mmol/L; and potassium, 76 mmol/L.

At the age of 3 years, genetic testing confirmed CCD, i.e., homozygous disease causing sequence variants. Of the nonsense mutation, c.559G>T; p.G187X in the exon 5 of the SLC26A3 gene was detected. Currently, the patient is still on salt supplement and is growing appropriately.

CASE 5

An infant girl was born at 36 weeks gestation (BW, 2.9 kg) through CD due to polyhydramnios and cord prolapse. AUS showed DBL. She did not pass meconium for 24 h after birth.

Subsequently, she developed AD, VBL, and sluggish bowel sounds. However, barium enema was not conclusive. As the patient did not improve, at 11 days, she underwent laparotomy and decompression ileostomy (a DBL down to terminal ileum was found).

However, no mechanical obstruction was identified and IO was suspected. At 16 days, she had multiple colon biopsies showing normal immature ganglion cells. Six months later, the ileostomy was closed and chronic diarrhea was documented for the first time.

One year later, she was developmentally delayed and with multiple hospital admissions due to diarrhea and dehydration;

she was admitted for gastroenteritis. Initial serum sodium was 136 mmol/L; potassium, 2.5 mmol/L; chloride, 82 mmol/L; and CO_2, 35. Urea was 16.1 mmol/L and creatinine was 61 mmol/L. SE showed potassium, 41 mmol/L; sodium, 60 mmol/L; and chloride, 105 mmol/L.

The child was started on oral salt supplements and her electrolytes improved (potassium, 4 mmol/L; CO_2, 26 mmol/L; sodium, 137 mmol/L; and chloride, 106 mmol/L). No confirmatory genetic testing was performed for this patient. She was lost to follow-up at the age of 14 years.

DISCUSSION

The elements to diagnose CCD include typical AUS findings, typical post-natal serum electrolyte disturbances, and typical SE findings. Furthermore, confirmatory genetic testing is available (2): SLC26A3 gene on chromosome 7q31. Of the many mutations similar to those in our tested patients, G187X is the most common mutation among Arabs and Saudis (1,7). Unfortunately and despite the above, multiple diagnostic challenges exist, such as misinterpreting watery diarrhea as urine (3,4). Of the others, we will address challenges faced in our cases.

Previous reports have proposed antenatal diagnosis of CCD relying on typical AUS findings, namely, polyhydramnios and DBL (3). These and metabolic abnormalities were considered evidence of intrauterine diarrhea (2-4). Nevertheless, they may indicate fetal IO requiring rectal biopsy (1,2,8). However, studies have found that a generalized bowel loop dilatation, normal peristalsis, and polyhydramnios favor CCD rather than IO (9,10). Of note, if IO is suspected, some of the bowel loops would be dilated, as the obstruction is most often proximal to the ileum (10). Moreover, amniocentesis will show high concentrations of gamma-glutamyl transpeptidase and alkaline phosphatase secreted by the ileum in CCD patients (11). Therefore, antenatal findings may have a role in the early CCD diagnosis.

In contrast and upon reviewing the literature, cases of CCD misdiagnosed as surgical conditions were sparsely reported. In 1983, Lundkvist et al. (12) reported 3 infants with CCD: 2 were misdiagnosed initially as HD, while one patient presented with volvulus post diagnosing CCD. All had stoma formation. They explained intermittent AD in CCD because of intermittent mesenteroaxial twisting of intestine predisposing some patients to develop volvulus and malrotation similar to Case 2. However, no explanation of IO picture could be found in the other cases. We hypothesize it may be related to electrolyte imbalance.

In the natural course of CCD, a neonate will have iso-osmolal dehydration initially, which then is converted to hypo-osmolal dehydration by the end of first week if not treated adequately. The classic metabolic disturbances described above usually develop after the age of 3 months (2). This may explain, partly, delayed CCD diagnosis in Case 4, despite positive family history and other typical features.

Chronic dehydration and renal impairment is a known complication of CCD (7, 8). However, chronic dehydration can cause low fecal chloride concentration (reaching <40 mmol/L) (2) necessitating repeated fecal examinations. A feature not seen in our cases. Lack of severe dehydration in our cases or missing the periods of severe dehydration may be an explanation. Hence, having a high index of suspicion and repeated SE may improve the yield of investigations.

In 1971, Arronson (13) described 3 patients with "secondary" chloride diarrhea after surgical intervention. First and third patients showed spontaneous recovery, while the second patient underwent 2 laparotomies for IO with colostomy formation. She had profuse diarrhea and died. The scenario raised our concerns of unrecognized CCD. It had similarities with Case 5.

Congenital chloride diarrhea screening recommendations varied among different reports. One report suggested testing those who have typical antenatal findings and no post-natal evidence of bowel obstruction (1). Another report recommended screening all children with a positive family history and those with nonspecified malabsorption condition (14). We recommend a simultaneous evaluation for both IO and CCD, one being a serious life-threatening condition, while the other may lead to catastrophic situation, if not diagnosed and managed appropriately.

Finally, our cases had a delayed diagnosis and mismanagement at their referring centers due to lack of awareness toward this differential diagnosis therefore, we recommend educating the staff, particularly at remote institutes. One strategy would be providing feedback to the referring hospitals to prevent further missed cases, as we did with our cases.

In this report, we highlighted different unusual presentations of CCD. Those patients had multiple diagnostic challenges as outlined above. Pediatricians, particularly in peripheral hospitals, must maintain a high index of suspicion for neonates and infants presenting with a picture of IO. Instituting screening programs may help in early diagnosis.

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