

## Clinical Report

# Acute pre-renal failure: acquired chloride diarrhea after bowel resection

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### Abstract

A 58-year old male with a history of small bowel resection and ileostomy presented with severe dehydration and high ostomy output. Laboratory investigation indicated hypochloremia, hypokalemia, hyponatremia, metabolic alkalosis, chloride-rich diarrhea, acute renal failure, and low urinary chloride excretion. Due to striking similarities to congenital chloridorrhea (CCD) reported in neonates, we empirically diagnosed acquired chloridorrhea (ACD, chloride diarrhea). This is a rare disorder resulting in profuse chloride-rich diarrhea and classic metabolic derangements affecting adults with chronic intestinal inflammation, often in association with bowel surgery. In this report, we review the relevant literature and discuss the genetic defects likely contributing to both the congenital and acquired forms of chloridorrhea.

**Keywords:** acquired chloridorrhea; chloride-rich diarrhea; chloridorrhea; congenital chloridorrhea

### Introduction

Acquired chloridorrhea (ACD) is a rare disorder presenting with chloride-rich diarrhea, severe volume depletion, metabolic alkalosis, hypochloremia, hypokalemia, hyponatremia, acute renal failure, and low urinary chloride excretion. This array of derangements is also seen in congenital chloridorrhea (CCD) [1], a neonatal disorder that generally incurs death by the third decade of life [2]. Although CCD has been described ~100 times in the literature [2, 3], the acquired form is still elusive and may be seen with severe intestinal stress or surgery.

### Case description

A 58-year-old African American male presented with profuse diarrhea and severe dehydration after right hemicolectomy, extensive distal ileal resection, ileostomy, and colostomy placement post-small bowel incarceration 9 weeks before. Ileostomal output approximated 3 L of watery stool per day despite diphenoxylate with atropine and loperamide therapy. He reported salt craving but denied vomiting, diuretic use, pain, or persistent childhood diarrhea. His vital signs were temperature 98.8 F, respiratory rate 20, pulse 89, and blood pressure 97/71 mmHg. On examination, he was found to be tachycardic and demonstrated postural hypotension. He looked cachectic. His abdomen was soft with ileostomy and colostomy bags draining liquid stool.

As shown in Table 1, initial laboratory values demonstrated hyponatremia, hypochloremia, hypocalcemia, hyperphosphatemia, hypomagnesemia, acute renal failure, and surprisingly, metabolic alkalosis. Urine studies revealed low sodium and chloride excretion in urine suggesting gastrointestinal origin of the metabolic alkalosis. Stool studies for *Clostridium difficile* toxin, fecal leukocytes, fecal ova, and parasites were negative. HIV ELISA (Human immunodeficiency virus enzyme linked immunosorbent assay) for 1 and 2 were nonreactive. Vasoactive intestinal protein was normal. After initial fluid replacement with normal saline, he developed hypokalemia (potassium 2.8 mEq/L). His fecal studies (ileostomal source) reported low pH with high fecal chloride. He was anemic with low iron and vitamin B12 stores. Over several days, he received 24 L of fluid and nutrient and electrolyte replenishment, but continued to have high ostomy output. Short bowel syndrome likely exacerbated nutritional deficiencies and increased gastric motility, thereby promoting high ostomy output [4].

During hospitalization, he improved with intravenous sandostatin (octreotide) and omeprazole which reduce gut motility and gastric hydrochloric acid losses. At discharge, hydration status, electrolyte abnormalities, and pre-renal failure normalized (Table 1), but he required two readmissions for similar, albeit less severe relapses. After surgical re-anastomosis, pathology reported only mild ileal and colonic mucosal inflammation and hyperemia. No genetic studies were performed. Two months post-operatively, the diarrhea resolved completely, electrolytes normalized, he was

**Table 1.** Relevant laboratory studies

Lab	Presentation (some values are after hydration)	2 months post-operation	Units
<b>Serum studies</b>			
Sodium	129	140	mEq/L
Potassium	3.7 <sup>a</sup>	4.0	mEq/L
Chloride	68	105	mEq/L
Bicarbonate	41	28	mEq/L
Calcium	6.6	9.8	mg/dL
Blood urea nitrogen	103	11	mg/dL
Creatinine	10.6	1.2	mg/dL
Phosphorus	6.2	-	mg/dL
Magnesium	1.3	1.4	mg/dL
Hemoglobin	10.4	10.6	g/dL
pH	7.545	-	-
pO <sub>2</sub>	79	-	mmHg
pCO <sub>2</sub>	52.9	-	mmHg
Base excess	21.8	-	mmol/L
Alkaline phosphatase	298	122	U/L
AST	45	28	U/L
ALT	84	37	U/L
Total protein	7.6	6.5	-
Albumin	4.1	3.3	-
Ferritin	X	352	-
B12	150.6	-	-
<b>Spot urine studies</b>			
Creatinine	122.9	-	mg/dL
Sodium	<20 <sup>b</sup>	-	mEq/L
Potassium	87.6	-	mEq/L
Chloride	<20 <sup>c</sup>	-	mEq/L
<b>Fecal studies (ileostomy source)</b>			
Consistency	Watery	-	-
Volume	3-4 L	-	-
pH	6.0 to 6.5 <sup>d</sup>	-	-
Sodium	119	64	mEq/L
Potassium	9	10	mEq/L
Chloride	100	73	mEq/L
Osmolarity	307	346	mOsm/kg

<sup>a</sup>Potassium decreased to 2.8 mEq/L after initial fluids.

<sup>b</sup>Our lab does not report urinary sodium <20.

<sup>c</sup>Our lab does not report urinary chloride <20.

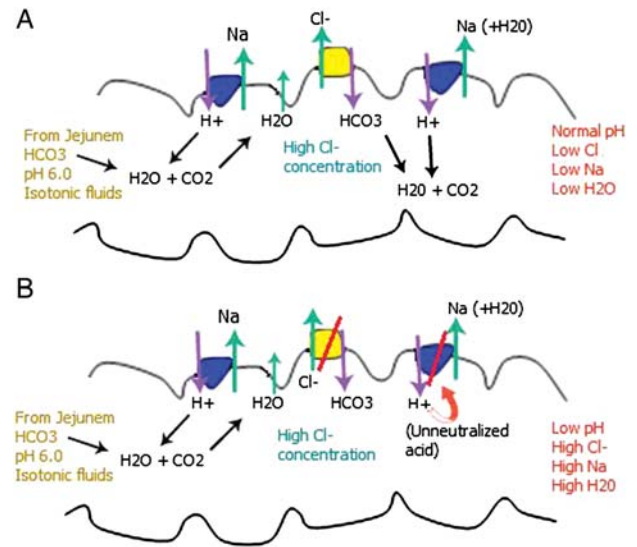
<sup>d</sup>The pH (6.0-6.5) in the fecal (and ileal collections) represents a low bicarbonate concentration, where naturally a higher HCO<sub>3</sub><sup>-</sup> concentration would be expected in fecal fluids. AST, aspartate aminotransferase; ALT, alanine aminotransferase.

gaining weight, and octreotide and omeprazole were successfully discontinued.

## Discussion

CCD was first recognized in 1945, but only recently have the causative CLD gene and its defective gene product, DRA (down-regulated in adenoma), been characterized [5, 6]. DRA is a chloride-bicarbonate (or hydroxide) (Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup>) membrane transporter anion exchanger found in distal ileal and colonic brush borders. Figure 1a and b show pertinent pathophysiology. All reported cases of CCD demonstrate fecal chloride >90 mEq/L with half of the cases exhibiting fecal chloride concentrations greater than the sum of fecal potassium and sodium [3, 7].

Renal insufficiency due to volume contraction is common [7, 8] though other associated renal lesions have been described [3]. Although CCD is a disease of the young, diagnosis may be delayed if the patient copes by increasing salty food consumption [9].



**Fig. 1.** (A) Normal jejunal effluent enters the ileum and hydrogen-sodium transporters secrete hydrogen ions and reabsorb sodium and water. This promotes luminal water formation leaving luminal chloride concentrations unchanged (hence relatively concentrated). Normal DRA transporters (1) absorb chloride, and (2) secrete HCO<sub>3</sub><sup>-</sup> (or OH<sup>-</sup>) (Kere) which reacts with protons, thereby neutralizing pH and forming water to be absorbed distally. (B). In CCD and ACD, dysfunctional DRA cannot absorb chloride or secrete bicarbonate resulting in loss of chloride-, acid-, and water-rich fluid to the environment. This causes hyponatremia, metabolic alkalosis, and volume depletion (3). Additionally, hyponatremia and hypochloremia develop despite avid yet insufficient renal retention, contraction alkalosis, and elevated aldosterone secretion promoting renal potassium losses [1].

However, severe disease states are unlikely to be asuaged by diet alone, making milder or clinically silent mutations in otherwise healthy persons likely [10]. Unfortunately, neither heterozygous phenotypes nor mutations manifesting with bowel stress (i.e. bowel resection) are known.

In contrast to CCD, our previously healthy adult patient presented with acquired chloridorrhea. Acquired and congenital cases differ in that ACD (i) responds partially to potassium replacement, (ii) may have small quantities of chloride in the urine rather than zero often reported in CCD [11], (iii) appears to be associated with bowel resections and ostomies, and (iv) can be transient and reversible with surgical correction of the bowel abnormality.

In 1954, Ariel [11] reported the first case of ACD in a 66-year-old male post-colectomy with colostomy presenting with copious, chloride-rich diarrhea and hypochloremic, hypokalemic alkalosis, hypokalemia, and metabolic alkalosis. Intravenous saline partially corrected serum electrolytes and potassium repletion resulted in dramatic improvement. Twenty years later, Bieberdorf *et al.* [12] demonstrated that perfusing normal colons with a chloride-poor solution rich in non-absorbable ions reproduced diarrhea and electrolyte changes found in chloridorrhea, demonstrating an inducible, complex defect requiring more than potassium repletion alone. Other reports of ACD include that of a 39-year-old Crohn's patient with intestinal transplantation and ileostomy [13] and three infants with intestinal obstruction and ostomy placements [8, 14].

Ostomies are not uncommon, but the rarity of chloridorrhea suggests an underlying genetic predisposition

evident only with significant bowel stress. Yang *et al.* demonstrated in animal models that chronic intestinal inflammation promotes extensive cytokine release resulting in reduced DRA expression, altered epithelial permeability and electrolyte transport, and induction of intestinal chloride loss and associated electrolyte abnormalities [6]. Our tissue sample was processed in Columbus, Ohio, USA. Reverse transcription-polymerase chain reaction (RT-PCR) for DRA expression was not available at the facility. To continue to produce large volume (diarrheal) fluid, there is a need for high deliveries of Na<sup>+</sup> and Cl<sup>-</sup> to the ileum. This, in turn, requires good splanchnic blood flow and adequate extracellular fluid (ECF). Much like a cholera patient, ECF expansion during treatment paradoxically can worsen the volume of diarrhea.

The treatment of CCD and ACD has been generally disappointing, though ACD can be transient. Marx *et al.* [8] reported that addition of proton-pump inhibitor (PPI) therapy improved the symptoms in a Crohn's patient with ACD. The PPI blocks gastric hydrochloric acid and chloride secretion, thereby reducing luminal losses to the environment when DRA is dysfunctional [8]. Octreotide (Sandostatatin) is useful in nonspecific treatment of different forms of secretory diarrhea (including verner morrison syndrome and CCD) because of its antimitility and inhibitor effects on small intestinal secretion [9]. While PPI (omeprazole) and octreotide therapy improved our patient's clinical status until he received corrective surgery, after surgery his disease resolved and further medication was no longer necessary.

## Conclusion

In summary, ACD presents with profuse, chloride-rich diarrhea and a surprising contraction metabolic alkalosis rather than metabolic acidosis often associated with typical diarrhea. ACD and CLD may represent a disease spectrum, resulting from insult to the same gene product, DRA. The available literature suggests that chronic intestinal inflammation and reduction of DRA expression in genetically susceptible persons post-bowel resection and ostomy placement may result in ACD. Although ACD is rare, it is likely under-recognized in post-bowel resection patients, and requires accurate identification in order to implement appropriate treatment.

*Conflict of interest statement.* None declared.

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