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Favorable Effects of Octreotide in Congenital Chloride Diarrhea Associated With CKD

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INTRODUCTION

Congenital chloride diarrhea (CCD) is a rare autosomal recessive disorder caused by mutations in the solute carrier family 26-member 3 (*SLC26A3* alias DRA) gene on chromosome 7q31. Over 250 cases of CCD have been reported in the literature with the highest incidence in the Arabian Peninsula, likely due to a high rate of consanguinity.[1]

Failure of the bowel to absorb chloride as a result of loss of function of the chloride ion (Cl^-)/bicarbonate ion ($HCO3^-$) exchanger leads to fecal loss of chloride together with sodium (Na^+) and potassium (K^+) anions and water. This manifests as chronic hypovolemia, hypokalemia and metabolic alkalosis. The mainstay of treatment for CCD is lifelong fluid and electrolyte substitution. This helps to replenish fluid and electrolytes but does not relieve the chronic diarrhea, which nonetheless tends to improve with time. Attempts to reduce the diarrhea by cholestyramine, butyrate and proton pump inhibitors have been met with variable results. Chronic diarrhea is associated with isolation, mental health problems and poor quality of life in a number of disorders.[2,3]

A quarter of patients with CCD develop chronic kidney disease (CKD) as a result of decreased renal perfusion, hypokalemia, and activation of the renin-aldosterone angiotensin axis,[4] and some patients progress to end stage renal disease necessitating renal replacement therapy.[5] Persistence of chronic hypovolemia as well as hypokalemia and metabolic alkalosis into advanced stages of CKD and end stage renal disease poses unique management challenges.

Chloride, the main extracellular anion, has important physiological functions including maintaining plasma osmolality, acid-base balance and cell signaling. Daily intake of chloride is about 100 mmols.[6] Chloride is both secreted and absorbed by the gut. Several mechanisms are involved in intestinal sodium chloride absorption including both electroneutral and electrogenic processes. Somatostatin receptors are present in the human intestines[7] and the synthetic somatostatin analog octreotide has been shown to decrease chloride secretion in the jejunum and to increase net fluid absorption. The result can be a dramatic reduction in stool volume.[8]

Herein, we present 3 patients with CCD caused by the Saudi founder mutation SLC 26A3 variant c.559G>T (p.G187), who developed progressive CKD and were referred to the nephrology service. Two of the 3 had been on oral electrolyte solution (OES). Following informed consent, octreotide acetate long-acting depot formulation (Octreotide LAR) was administered to all 3 with biochemical and clinical improvement.

CASE PRESENTATION

Patient 1

Patient 1 is a 25-year-old male born at 36 weeks gestation to a consanguineous couple with no family history of CCD. He presented with refractory diarrhea and frequent dehydration. The diagnosis of CCD was

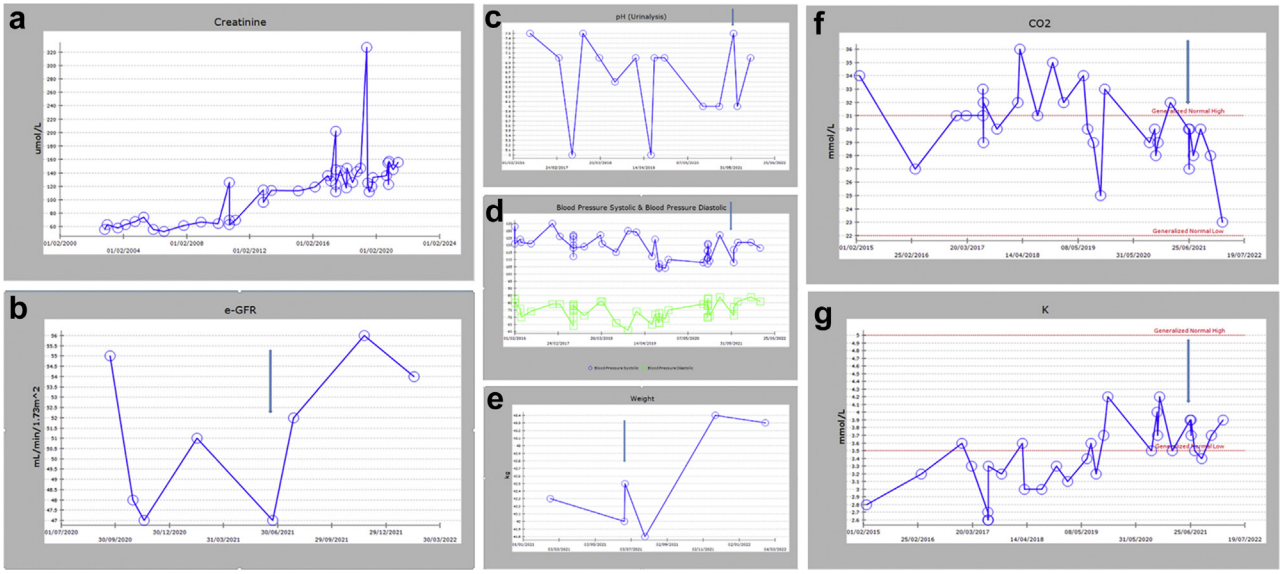

Figure 1. Case 1 (patient 1) clinical and laboratory changes before and after treatment with octreotide. Creatinine levels preoctreotide showing the progressive trajectory before treatment with superimposed AKIs (a); eGFR before starting octreotide showing progressive decline with episodes of AKI and the improvement after octreotide initiation (b); Urine pH (c); Blood pressure (d); Weight (e); CO_2 (f); K (g). Blue arrow, Octreotide initiation. AKI, acute kidney injury; CO_2, carbon dioxide; eGFR, estimated glomerular filtration rate; K, potassium.

established by an elevated stool chloride concentration at the age of 4 months. OES therapy was initiated. Genetic testing revealed homozygous *SLC26A3* variant c.559G>T (p.G187*). He had frequent hospitalizations because of dehydration and acute kidney injury (AKI) and went on to develop CKD. When seen by nephrology, his serum creatinine ranged from 110 μmol/l to 150 μmol/l and urine protein-creatinine ratio fluctuated between 11.5 mg/mmol to 194 mg/mmol. He was diagnosed with gout at the age of 24 years. Three episodes of AKI were documented in our hospital (Figure 1). He complained of voluminous diarrhea (5–6 bowel motions/day), fecal soiling, and nocturnal enuresis. Medications included potassium chloride, sodium chloride, allopurinol, and cholecalciferol. Height and weight were 0.1% for the age of 20 years (FAT). He was started on monthly 20 mg i.m. Octreotide LAR depot injections. Diarrhea frequency decreased to 2 to 3 per day. His body weight increased from 41.8 to 43.4 kg (+3.8%) (Table 1 and Supplementary Table S1). These changes were coupled with biochemical improvement as follows: serum potassium increased and bicarbonate ion decreased to 23 mmol/l (Figure 1) despite reduction in OES dose. He reported significant improvement in his quality of life. Diarrhea frequency was noted to increase when he missed his monthly Sandostatin LAR injection.

Patient 2

Patient 2 is a 25-year-old male with a history of chronic diarrhea. He was born full term to distant cousins with no family history of CCD. Diarrhea started early in life, and he underwent bowel resection at a young age for unknown reasons. He had frequent hospitalizations for dehydration due to diarrhea. Repeated gastrointestinal evaluation including endoscopies and biopsies failed to reveal the cause of his diarrhea. A referral was made to the intestinal transplant service for a diagnosis of "short bowel syndrome" which was ruled out. The presence of metabolic alkalosis suggested the diagnosis of CCD which was confirmed by an elevated stool chloride concentration of 161 mmol/l. Genetic testing revealed the same *SLC26A3* mutation as patient 1. The nephrology service was consulted for multiple AKI episodes (Supplementary Figure S1), with 1 requiring brief dialytic support. His weight was 0.1% and height 11% FAT. Serum creatinine was 240 μmol/l, estimated glomerular filtration rate was 32 ml/min, urea was 21.9 mmol/l, potassium was 2.9 mmol/l and urine protein-creatinine ratio was 36 mg/mmol. During his last AKI episode, venous blood gases showed serum bicarbonate of 67 mmol/l and a pH of 7.6. Medications included potassium chloride, allopurinol and sevelamer carbonate. Octreotide LAR 20 mg i.m. was administered every 4 weeks. Bowel movement frequency declined by 50%. His body weight increased by 2.2 kg (+4.9%) (Table 1 and Supplementary Table S1). He has not required hospitalization over a follow-up period of 6 months. His serum creatinine progressively declined to 207 μmol/l with estimated glomerular filtration rate (eGFR) increasing to 37 of ml/min). Serum potassium normalized on the same potassium chloride dose. Serum carbon dioxide normalized, and urine pH decreased from 8 to 6. His previously low blood pressure was noted to have

Table 1. Changes in biochemistry, blood pressure and body weight preoctreotide and postoctreotide

	Serum K (mmol/l)		Serum Cl (mmol/l)		Serum CO_2 (mmol/l)		Serum Creat (mmol/l)		Urine pH		Blood pressure (mm Hg)		Body weight (kg)	
Case	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	3.5	3.9	97	94	30	28	143	138	7.5	7	108/77	118/81	42	43.3
2	3.1	4	83	102	38	25	392	207	8.5	6	105/69	135/87	40.8	47

Cl, chloride; CO_2, carbon dioxide; Creat, creatinine; K, Potassium.

increased to 135/87 mm Hg during his last office visit with an increase in urine protein-creatinine ratio to 150 mg/mmol.

Patient 3

Patient 3 is a 17-year-old male who was born at 37 weeks gestation. A CCD diagnosis was established at the age of 7 months with elevated stool chloride and subsequently confirmed by genetic testing showing the same *SLC26A3* variant as patients 1 and 2. OES was initiated but he continued to suffer recurrent dehydration which persisted even after the insertion of a gastrostomy tube. He developed progressive CKD and received pre-emptive kidney transplantation at the age of 13 from his mother. Post-transplantation course was complicated by frequent episodes of dehydration, electrolyte imbalance, and seizures. Acute and chronic rejection, nephrocalcinosis and recurrent hypovolemic AKIs led to allograft failure within 2 years. Automated peritoneal dialysis was initiated at the age of 15 but his parents frequently skipped peritoneal dialysis to avoid associated fluid loss. Parathyroidectomy was performed at the age of 16 years for severe secondary hyperparathyroidism, which was followed by recurrent seizures resulting from a combination of hypocalcemia and severe metabolic alkalosis. Peritoneal dialysis prescription was modified to allow for a positive fluid balance. Octreotide LAR 20 mg i.m. once a month was commenced. His bowel movements decreased by 50%. Both his OES requirements (Supplementary Table S1) and serum carbon dioxide decreased (Supplementary Figure S2). He had no further emergency department visits or hospitalizations for dehydration or seizures.

DISCUSSION

Patients with CCD, as a result of their voluminous diarrhea, suffer from chronic hypovolemia, delayed growth, and increased risk of CKD. They also commonly suffer from fecal soiling and enuresis. These symptoms can compromise quality of life, lead to social isolation, and jeopardize chances of gainful employment. Although the standard treatment with OES improves growth outcomes, chronic diarrhea persists. Current therapies to control diarrhea have limited or temporary efficacy.

Aichbichler *et al.*[9] reported a 34-year-old man diagnosed with CCD and diarrhea frequency of 6-12 stools per day. When omeprazole was added to OES therapy, stool frequency decreased to 2 to 4 per day and he was able to return to work. Pieroni and Bass[S1] used proton pump inhibitors in a neonate with CCD with good results. They treated their patient with i.v. pantoprazole followed by oral omeprazole 1 mg/kg per day. The patient maintained weight and height for her age and at 18 months was doing well without the need for OES.

Butyrate stimulates electroneutral absorption of sodium chloride by up-regulation of the sodium ion/hydrogen ion and Cl^-/bicarbonate ion transporters. They also activate the Cl^-/butyrate and sodium ion/hydrogen ion exchangers and reduce Cl^- secretion by inhibiting the sodium ion-potassium ion-$2Cl^-$ co-transporter (NKCC1). Canani *et al.*[S2] reported clinical and biochemical benefits of butyrate in a child with CCD, but a study using butyrate in 7 patients with different *SCL23A6* mutations showed variable responses.[S3] Variability in the response to butyrate was also reported[S4] in 5 Finnish patients with CCD. Butyrate therapy response appears to be genotype-dependent and may be ineffective with nonsense variants such as the G187.[S3] Cholestyramine can also cause short term improvement in diarrhea in patients with CCD.[S5]

Somatostatin is a 14 or 28 amino acid peptide secreted by D-cells in the stomach and pancreas. There are 5 subtypes of somatostatin receptors $SSTR_{1-5}$.[S6] Somatostatin analogues are used in refractory diarrheas of different etiologies.[S7] Octreotide acetate is a synthetic somatostatin analog commercially available in a long-acting depot form (Sandostatin LAR i.m. injection). Sandostatin has high affinity for SSTR2, moderate for SSTR5 and weak for SSTR3.[S8] It inactivates adenylate cyclase and prevents calcium ion or potassium ion efflux by inhibiting G proteins. This blocks the secretion of several gastrointestinal hormones such as gastrin, insulin, glucagon, secretin, vasoactive intestinal peptide, and motilin[S9] as well as chloride secretion[8] and enhances electroneutral sodium chloride absorption.

The long-acting formulation of octreotide acetate- LAR administered as a monthly i.m. depot injection reduced the number of bowel movements and increased weight and blood pressure in our patients. It also increased serum

Table 2. Teaching points

1 The presence of metabolic alkalosis and chronic diarrhea should raise the possibility of CCD even in adults.
2 Most of the chloride absorbed by the gut comes from gastric and intestinal secretions rather than form oral intake.
3 Failure of the intestines to absorb chloride results in metabolic alkalosis which can worsen with marked decrease in GFR.
4 CKD is a frequent complication of CCD.
5 Octreotide by reducing fecal chloride loss in patients with CCD can help ameliorate the associated hypovolemia, hypokalemia, and metabolic alkalosis.

CKD, chronic kidney disease; CCD, congenital chloride diarrhea; GFR, glomerular filtration rate.

potassium, decreased serum carbon dioxide levels, and/or reduced OES requirements. Patients 1 and 2 experienced a reduction in the frequency of emergency department visits and hospitalizations for dehydration and had no more seizures. This suggests that Sandostatin LAR is beneficial in patients with CCD with CKD.

The prevalence of CKD in CCD appears to increase in adult life and the long-term renal outcome remains unclear.[4,S10] In a study from Finland, 5 of 8 patients over the age of 30 years had CKD.[S10] Imaging findings include small kidneys, increased echogenicity and nephrocalcinosis.[4,S10,S11] Kidney biopsies from patients with CCD show juxtaglomerular hyperplasia, global glomerular sclerosis, interstitial fibrosis, tubular atrophy, and arteriolopathy.[S12,S13] Nephrocalcinosis secondary to calcium phosphate deposition is the main feature of kidney injury.[S10,S11] Segmental sclerosis has also been described.[S14] The reason for kidney disease in CCD is multifactorial. These patients suffer from intrauterine growth retardation and are often born premature, and both conditions can contribute to low nephron endowment.[S15] Chronic dehydration and frequent episodes of AKI, as we have documented in patients 1 and 2, increase their risk of CKD. Patient 3 also had multiple episodes of hypovolemic AKI after his transplantation and his allograft failed prematurely. Phosphaturia has been shown to occur in rats suffering from dietary chloride depletion and may contribute to nephrocalcinosis in patients with CCD.[S16]

Our report has several important limitations including its retrospective nature, the small number of patients, lack of a control group, and limited duration of therapy. Confounding factors include suboptimal treatment adherence in patients 1 and 2 and dialysis-related volume, electrolyte and acid-base changes in patient 3. The fact that favorable changes were still evident in the first 2 patients despite optimal adherence supports a treatment effect.

In conclusion, we report 3 patients with CCD and CKD who achieved a reduction in their stool volume with Sandostatin LAR treatment together with measurable improvements in their volume status, electrolytes, and alkalosis. The parenteral route and the long dosing interval may improve adherence especially in children and adolescents. The role of somatostatin analogues in the treatment of CCD deserves further study (Table 2).

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

Written informed consent was obtained from all patients.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

Figure S1. Case 2 (MS) clinical and laboratory changes before and after treatment with octreotide

Figure S2. Case 3 (AS) clinical and laboratory changes before and after treatment with octreotide

Table S1. Changes in the bowel motion frequency and oral electrolyte doses pre and post octreotide

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