Renal abnormalities in congenital chloride diarrhea

Nadia M. Al-Hamad, FRCP(c), FAAP, Amal A. Al-Eisa, MRCPCH, FRCP.

ABSTRACT

Congenital chloride diarrhea (CLD) is a rare autosomal recessive disorder caused by a defect in the chloride/bicarbonate exchange in the ileum and colon. It is characterized by watery diarrhea, abdominal distension, hypochloremic hypokalemic metabolic alkalosis with high fecal content of chloride (>90 mmol/l). We report 3 patients with CLD associated with various renal abnormalities including chronic renal failure secondary to renal hypoplasia, nephrocalcinosis and congenital nephrotic syndrome.

Case Report.

Patient One. A 10-month-old Kuwaiti boy presented with chronic watery diarrhea, poor weight gain and periorbital edema. He was a product of preterm delivery at 34 weeks of gestation. No abnormalities were reported in antenatal ultrasounds carried out repeatedly throughout pregnancy and no amniocentesis was performed during pregnancy. His birth weight was 2.3 kg and his apgar score was 6 at one minute and 9 at 5 minutes. He had no significant immediate neonatal problems. He was a poor feeder and was gaining weight very slowly from birth. A chronic diarrhea of watery stools was reported at the age of 3 months for which he was admitted once to a peripheral hospital and treated as a case of gastroenteritis. At presentation, the child was moderately dehydrated and pale. His weight and height were below the third percentile while his head circumference was on the 25th centile. His heart and chest examinations were unremarkable. He had moderate abdominal distension but there...
was no evidence of hepatosplenomegaly, ascites or palpable kidneys. He had normal genitalia and there was no evidence of peripheral edema. His investigations on admission showed: hemoglobin of 132 gm/L, white blood cell count of 6.5 10^9/L, platelets of 230 10^9/L, blood urea nitrogen of 1.3 mmol/L, creatinine of 34 µmol/L, potassium 2.3 mmol/L, sodium 130 mmol/L and chloride 82 mmol/L. An arterial blood gas analysis showed a pH of 7.51, bicarbonate 34 mmol/L, carbon dioxide of 3.2 kilopascal (kPa), partial pressure of oxygen of 15 kPa and a base excess of 12. His serum calcium was 1.8 mmol/L, serum phosphorus 1.9 mmol/L, serum uric acid 329 µmol/L, plasma total protein of 51 gm/L and serum albumin 11 gm/L. His liver enzymes were within normal range and his cholesterol level was 9.3 mmol/L, triglycerides was 3 mmol/L. His urine analysis showed a specific gravity of 1.020, protein of 5 gm/L, red blood cells of 50 per high power field (hpf) and white blood cells of 2/hpf. There was no evidence of glucosuria or ketonuria. His urinary protein loss was 7.3 grams per 24 hours. His fecal chloride level was 123 mmol/l and 140 mmol/l on 2 occasions and his fecal sodium was 95 mmol/l and potassium was 27 mmol/l. Ultrasound of the kidneys showed a kidney size of 6 cm on each side, with increased echogenicity of both kidneys with preservation of cortico-medullary differentiation. His kidney biopsy showed variable degrees of global sclerosis in 70% of the glomeruli with mild to moderate mesangial cell expansion. No fibrinoid necrosis was seen and the basement membrane was not thickened or spiked. Moderate degree of tubular atrophy, interstitial fibrosis and focal chronic inflammation were observed with generalized nephrocalcinosis. Blood vessels were healthy. Immunofluorescence showed no deposits (Figure 1). The child was commenced on potassium chloride supplements orally and a course of daily dose steroids were tried in a dose of 60 mg per square meter of body surface per day. No response to steroids was noted after 8 weeks of daily treatment. No cytotoxic drugs were tried for his nephrotic state as per his parent’s wish. The child continued to gain weight slowly in spite of potassium supplements and supportive medical treatment for his nephrotic syndrome including captopril, indomethacin and regular albumin infusions. At the age of 5-years his renal function started to deteriorate reaching end stage at the age of 5-years and 10-months. He was started on peritoneal dialysis awaiting transplantation.

**Patient 2.** A 13-year-old Kuwaiti boy was referred from a peripheral hospital for further management of his chronic renal failure. He was born at 33-weeks of gestation by spontaneous vaginal delivery after an uneventful antenatal period except for polyhydramnios confirmed by antenatal ultrasound. No amniocentesis was performed during pregnancy. His birth weight was 2 kg and his apgar score was 7 at one minute and 9 at 5 minutes. Abdominal distension was noticed at birth. He was passing watery stools from birth. His biochemical work up carried out at the age of 2-months showed a serum sodium of 130 mmol/L, serum potassium 2.6 mmol/L, serum chloride of 88 mmol/L, blood urea of 6.2 mmol/L and a serum creatinine of 129 µmol/L. Uric acid was 548 µmol/L. His blood gas analysis confirmed the presence of metabolic alkalosis (pH 7.52, bicarbonate of 32 mmol/l and base excess of 18). His urinary electrolytes were within normal range while 2 stool samples confirmed the presence of high fecal chloride (110 and 125 mmol/l), fecal sodium was 102 mmol/l and potassium was 27 mmol/l. Ultrasound of the kidneys showed a kidney size of 6 cm on each side, with increased echogenicity of both kidneys with preservation of cortico-medullary differentiation. His kidney biopsy showed variable degrees of global sclerosis in 70% of the glomeruli with mild to moderate mesangial cell expansion. No fibrinoid necrosis was seen and the basement membrane was not thickened or spiked. Moderate degree of tubular atrophy, interstitial fibrosis and focal chronic inflammation were observed with generalized nephrocalcinosis. Blood vessels were healthy. Immunofluorescence showed no deposits (Figure 1). The child was commenced on potassium chloride supplements orally and a course of daily dose steroids were tried in a dose of 60 mg per square meter of body surface per day. No response to steroids was noted after 8 weeks of daily treatment. No cytotoxic drugs were tried for his nephrotic state as per his parent’s wish. The child continued to gain weight slowly in spite of potassium supplements and supportive medical treatment for his nephrotic syndrome including captopril, indomethacin and regular albumin infusions. At the age of 5-years his renal function started to deteriorate reaching end stage at the age of 5-years and 10-months. He was started on peritoneal dialysis awaiting transplantation.

**Patient 3.** A Kuwaiti boy who was referred to our renal unit at the age of 3-years for further evaluation. He was a product of preterm spontaneous vaginal delivery at 29-weeks of gestation. Polyhydramnios was diagnosed antenatally both clinically and by ultrasound. No amniocentesis was carried out. His birth weight was 1.5 kg and his apgar score was 3 at one minute and
Renal abnormalities in CLD ... Al-Hamad & Al-Eisa

Discussion. Congenital chloride diarrhea is an autosomal recessive intestinal disease. The primary defect of the metabolic abnormalities manifested in the disease is caused by the absence or impairment of active chloride/bicarbonate exchange in both ileum and colon. Various studies have reported different incidence rates of CLD according to geographical regions. Incidence rate ranges from 1:43000 in Finland to 1:3200-13000 in Kuwait and 1:5500 live birth/year in KSA. The high incidence of CLD among Arab communities might reflect a high gene carrier state enhanced by consanguineous marriages which are very common in our communities. Mutations in the downregulated adenoma gene (DRA [MIM 1266501]) had been recently found to cause CLD. Until 1998, approximately 19 mutations in the CLD gene has been identified in patients with CLD in several different populations. Genetic studies carried out on 5 Kuwaiti CLD patients and 6 of their parents have shown that the most frequent Kuwaiti mutation was a G-T transversion at nucleotide position 559 with a predicted amino acid change. A substitution of glycine by the termination codon at 187 (G187X). The defective absorption of chloride results in osmotic diarrhea. Excessive fluid losses will subsequently lead to hypovolemia and intravascular volume contraction. Hypovolemia will activate the renin angiotensin aldosterone system leading to high renin and secondary hyperaldosteronism. The classical clinical presentation of such children manifests antenatally with dilated bowel loops on ultrasound and polyhydramnios leading to premature labor. In the newborn period, affected babies presents with watery diarrhea associated with hypotension and hypochloremia and slight metabolic acidosis. It then progresses to hypochloremic, hypokalemic metabolic alkalosis. Diagnosis is usually confirmed by fecal chloride concentration exceeding 90 mmol/L.

7 at 5 minutes. He was kept in the special care unit till he reached the weight of 2 kg. At the age of 4-months he was admitted with severe dehydration secondary to gastroenteritis. During admission his lab results revealed the presence of persistent hypochloremic hypokalemic metabolic alkalosis with hyponatremia even after correction of his dehydration. Urinary electrolytes showed sodium 10 mmol/L, potassium 8 mmol/L and chloride 10 mmol/L. His fecal electrolytes were as follows: sodium 85 mmol/L, potassium 24 mmol/L and chloride 143 mmol/L. The diagnosis of CLD was made and the child was started on sodium and potassium chloride supplements. During follow up, the child had repeated attacks of urinary tract infections. Ultrasound of the abdomen showed increased echogenicity of both kidneys with loss of cortico-medullary differentiation. The right kidney measured 6.2 cm in length and the left measured 6.5 cm (Figure 3). Further investigations showed a serum creatinine 52 µmol/L, blood urea nitrogen 5.5 mmol/L, calcium 2.7 mmol/L, phosphorus 2.1 mmol/L, uric acid 156 µmol/L, intact parathyroid hormone 2.1 pmol/L. His urine calcium creatinine ratio was 0.7. A 24-hour urine collection revealed creatinine of 18.8 µmol/L, calcium 4.4 mmol and urinary oxalate 10 mg/day. Peripheral plasma renin activity 6.12 pmol/L/s (range 0.04-0.52 pmol/L/s in resting position) and his serum aldosterone level was > 2.8 nmol/L (range 0.02-0.42 in supine position). A micturition cystourethrogram revealed no vesicoureteric reflux. A renal biopsy showed partial sclerosis of 8 glomeruli with periglomerular fibrosis. Tubules showed calcific deposits extending into the interstitium. Blood vessels were normal. Immunofluorescence was negative for all immunoglobulins, fibrin and complement. During 4 years of follow up, the child continues to maintain normal renal function with a fairly controlled serum electrolytes on potassium and sodium chloride supplements.
Renal involvement in CLD have been documented previously. It includes hyalinized glomeruli, nephrocalcinosis, medial arteriolar hypertrophy and juxtagonal hyperplasia resembling those seen in hypertensive disease. The hypertensive vascular changes results from the long standing hypovolemia leading to juxtagonal hyperplasia and subsequently leading to hyperreninemia and secondary hyperaldosteronism. In spite of the high levels of aldosterone, normovolemia is difficult to maintain due to the constant loss of both water and salt through the intestine. These vascular changes are usually seen in advanced stages of benign arteriolar nephrosclerosis and other hypertensive disorders associated with vascular alterations. Due to the constant state of hypovolemia, hypertension is not seen in spite of the high angiotensin activity that leads to chronic hypovolemia, hypertension is not seen in spite of the vascular alterations. Due to the constant state of hypovolemia, hypertension is not seen in spite of the vascular alterations.

Potassium loosing nephropathy has been described leading to tubulopathy and hypothrenuria aggravating fluid losses. Histologically, this is evident by the presence of vacuolization of the proximal convoluted tubular cells. Maintaining a normal serum potassium levels can lead to reversal of these abnormalities. Nephrosclerosis was described previously as a complication of a long standing disease, nevertheless, diffuse mesangial sclerosis presenting with infantile nephrotic syndrome has not been previously described with CLD. Diffuse mesangial sclerosis is a well known cause of congenital nephrotic syndrome which has been extensively characterized by Habib. Renal hypoplasia has been defined as a reduction in the number of nephrons and ducts or decreased nephron size with normal development and differentiation of those nephrons and ducts that are present. Generally, hypoplasia is regarded as non-genetic, although, it can be part of malformation syndrome and several autosomal syndromes. In these cases, it is not clear whether hypoplasia is a primary manifestation of the syndrome or merely secondary to generalized growth failure. The severe renal lesions do improve with optimal electrolytes and fluid replacement and ensuring good compliance of patients. On the contrary, failure to do so impairs kidney growth causing hypoplasia and subsequently subnormal filtration rate. Nephrocalcinosis occurs as a result of metabolic alkalosis leading to alkaline urine which predisposes to deposition of calcium phosphate and oxalate salts and appearance of calcification in the distal convoluted tubules. Alkalinity of urine and renal calcifications are the likely factors responsible for the increased susceptibility to urinary tract infection. Hyperuricemia occurs in some patients due to the reduction of urate clearance as a result of high angiotensin activity, which reverses back to normal with adequate control. Spironolactone has been used in reducing potassium chloride requirements with some success, while the use of prostaglandin synthetase inhibitors were of no help.

In conclusion, renal abnormalities should be looked for and monitored closely in patients with CLD as such abnormalities might determine the overall outcome of the disease. The genetic pattern of CLD in the Arabian Peninsula needs to be studied in more extensive way to delineate the association of its gene with genetic renal diseases.

References

Renal abnormalities in CLD ... Al-Hamad & Al-Eisa