Case report

Child Kidney Dis 2016;20:83-87
DOI: https://doi.org/10.3339/jkspn.2016.20.2.83

ISSN 2384-0242 (print)
ISSN 2384-0250 (online)

A Case of Secondary FSGS due to Chronic Chloride Diarrhea

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Received: 17 August 2016
Revised: 12 September 2016
Accepted: 10 October 2016

Congenital chloride diarrhea (CLD) is a rare autosomal recessive disease that is difficult to diagnose. CLD requires early treatment to correct electrolyte imbalance and alkalosis and to prevent severe dehydration. Renal injury is clearly associated with defective electrolyte balance induced by CLD, particularly during the first months or years of life. A 7-year-old boy was diagnosed with CLD following detection of a homozygous mutation (c.2063-1G>T) in *SLC26A3* at 6 months of age. During treatment with electrolyte supplements, mild proteinuria was detected at 8 months of age, and is still present. Renal biopsy showed the presence of focal renal dysplasia, with metaplastic cartilage and mononuclear cell infiltration, calcification, and fibrosis in the interstitium. Up to two-thirds of the glomeruli exhibited global obsolescence, mostly aggregated in the dysplastic area. In non-dysplastic areas, the glomeruli were markedly increased in size and severely hypercellular, with increased mesangial matrix, and displayed segmental sclerosis. The marked glomerular hypertrophy with focal segmental glomerulosclerosis suggested a compensatory reaction to the severe nephron loss or glomerular obsolescence associated with renal dysplasia, with superimposed by CLD aggravating the tubulointerstitial damage.

Key words: Congenital chloride diarrhea, Renal complication, Focal segmental glomerulosclerosis, Renal dysplasia

Introduction

Congenital chloride diarrhea (CLD) is a rare disease with an autosomal recessive inheritance[1)]. The incidence is in the range of 1 in 30,000 to 40,000 live births in Finland, which accounts for approximately one-fifth of the 250 reported cases[2)]. The solute carrier family 26 member 3 (*SLC26A3*) gene causative of CLD encodes a Cl^-/HCO_3^- exchanger expressed mainly in the intestinal epithelium[3)].

CLD is an intestinal disorder of defective electrolyte transport characterized by chronic secretory diarrhea with high fecal chloride levels. Because of the intrauterine onset of diarrhea, CLD patients present maternal polyhydramnios and premature birth[4)]. Postnatally, profuse watery chloride-rich diarrhea leads to excessive loss of fluids, dehydration, and weight loss[5)]. Electrolyte imbalances such as hypochloremia and hyponatremia are usually accompanied by metabolic alkalosis, activation of the renin-angiotensin system, and

hypopotassemia[6]. If untreated, this metabolic imbalance with severe dehydration can be lethal in infancy[4].

During childhood, growth retardation, development delay, and progressive renal involvement are common complications of CLD[7,8]. The renal injury manifests as multiple changes in the hyalinized glomeruli, juxtaglomerular hyperplasia, vascular changes, and nephrocalcinosis[9]. According to past reports, the main feature of the renal injury is known as nephrocalcinosis, which is caused by urine supersaturation and crystal precipitation, with no hypercalciuria or nephrolithiasis[7].

This report describes a case of CLD with mild proteinuria in which renal biopsy showed renal dysplasia and focal segmental sclerosis (FSGS) with only patchy calcification.

Case report

A 6-month-old male patient was brought to the Korea University Guro Hospital for severe watery diarrhea and lethargy in June, 2008. The patient's diarrhea symptoms began immediately after birth, and had been continuous up to the writing of this report. There were no accompanying symptoms such as vomiting or fever. The patient was born with a birth weight of 2,780 g at 37 weeks' gestation and was normal for his gestational age, except for the polyhydramnios in the prenatal phase.

The patient weighed 5.7 kg at the time of admission to the hospital, which indicated weight below the third percentile corrected by age. His height and head circumference were 67.8 cm (50th percentile) and 41 cm (25th percentile), respectively, which were within normal ranges. In blood tests after hospitalization, the patient's serum sodium level was 125 mmol/L, potassium 3.1 mmol/L, and chloride 62 mmol/L Serum magnesium was also low, at 0.9 mg/dL. Severe metabolic alkalosis was observed on blood gas analysis, with a pH of 7.71 and HCO_3^- 43.0 mmol/L. Notably, the patient's serum renin and serum aldosterone were very high, at 47.3 ng/mL/hr (normal range 1.4-7.8) and 1,479.9 pg/mL (normal range 65-860), respectively. Serum blood urea nitrogen was slightly increased at 25.6 mg/dL, but the patient's kidney function was normal, with serum creatinine (Cr) being 0.34 mg/dL and, estimated glomerular filtration rate 82 mL/min/1.73m^2. Serum protein was 8.3 g/dL, and urine specific gravity was slightly increased at 1.025 on urine analysis. Proteinuria, hematuria, and hypercalciuria were absent (urinary protein/Cr 0.38 mg/mg, urinary Ca/Cr 0.04 mg/mg). However, with regards to urine electrolytes, Na^+, K^+, and Cl^- levels were decreased (<10 mmol/L, 22.5 mmol/L, <10 mmol/L, respectively). There was no abnormal findings from the fecal studies, yet the fecal electrolyte testing could not be proceeded due to lack of related devices and protocols in our hospital laboratory. After treatment, symptoms of dehydration and the blood tests improved, although diarrhea symptoms continued even at discharge from hospital. Thus, a genetic test was conducted in August, 2008, which detected a homozygous splicing acceptor site mutation in *SLC26A3* (c.2063-1G>T in intron[18]), leading to the diagnosis of CLD. This mutation is known as a common mutation in Korean patients with CLD[10].

Treatment with NaCl and KCl oral formulations was continued during the outpatient follow-up period. Proteinuria was detected when the patient was 10-months-old with spot urine protein to creatinine ratio of 1.38. Though mild hypochloremia (88 mmol/L) was detected on blood testing, both serum Na^+ and K^+ and the blood gas analysis were normal; the serum Cr was 0.28 mg/dL. The patient have maintained a level of serum Cr ranging from 0.4 to 0.7 mg/dL since the age of 6 months, and mild proteinuria continued until the age of seven (urinary protein/Cr 0.2-1.7 mg/mg). Due to the patient's mild proteinuria, a percutaneous ultrasound-guided renal biopsy was performed at 7 years of his age. His vital sign was stable without hypertension and blood tests were within normal range: a serum protein and albumin level of 7.1 g/dL and 4.4 g/dL, respectively. The renal ultrasonography showed no abnormal findings and 24hr urine protein was checked as 173.1 mg/day.

After the biopsy, the electrolyte supplement is currently maintained. His height and body weight are all below than 3rd percentile (118.3 cm and 19.8 kg). His blood pressure is stable between 50th and 90th percentile, and blood tests showed no abnormal findings. But proteinuria is steadily detected with a urinary protein/Cr, 0.57 mg/mg.

1. Renal pathology findings

In a biopsy core of renal cortex, an abnormal dysplastic focus is present separated by normal cortical areas showing

immature tubules and aggregates of small globally sclerotic glomeruli (Fig. 1A). Furthermore, metaplastic cartilage is shown together with calcification (Fig. 1B). In another cortical areas without dysplasia, seven glomeruli are observed. The glomeruli are markedly enlarged, measuring 250 μm in maximum diameter, and severely hypercellular involving mesangial cells. Mesangial matrix is also increased. Two glomeruli exhibit segmental sclerosis (Fig. 1C). By electron microscopy, the glomerular basement membrane measures up to 400 nm in average thickness having relatively smooth inner and outer contours. No electron-dense deposits are found. Epithelial cell foot processes remain relatively patent (Figure not shown). In non-dysplastic areas, tubules reveal focal moderate atrophy and loss with interstitial fibrosis. Rarely, tubular calcification is seen (Fig. 1D).

Discussion

Renal complications are known to occur relatively frequently in CLD patients. A previous study reported that chronic kidney disease occurs in 28% of CLD patients[7]. Based on previous study results, early diagnosis is essential in these conditions to delay the progression of CLD-related kidney complications. In addition, timely balancing of electrolytes through proper supplementation of NaCl and KCl, together with acid-base balance, and periodical evaluation of kidney functions delay disease progression[8,11]. However, kidney complications often progress in CLD patients despite proper treatments. Such progression has been reported in previous studies, even in cases with transplanted kidneys[7].

These CLD-induced kidney diseases are known to occur mainly in the form of nephrocalcinosis[7]. Reabsorption of calcium ions filtered by the kidney glomerulus occurs in the proximal tubule and thick ascending loop of Henle (ThALH). Calcium reabsorption in this region occurs through passive para-cellular routes promoted by Na^+ and Cl^- reabsorption. The distal nephron accounts for only 10% of calcium reabsorption[12,13]. CLD patients fall into a continuous state of hyponatremia and hypochloremia as a

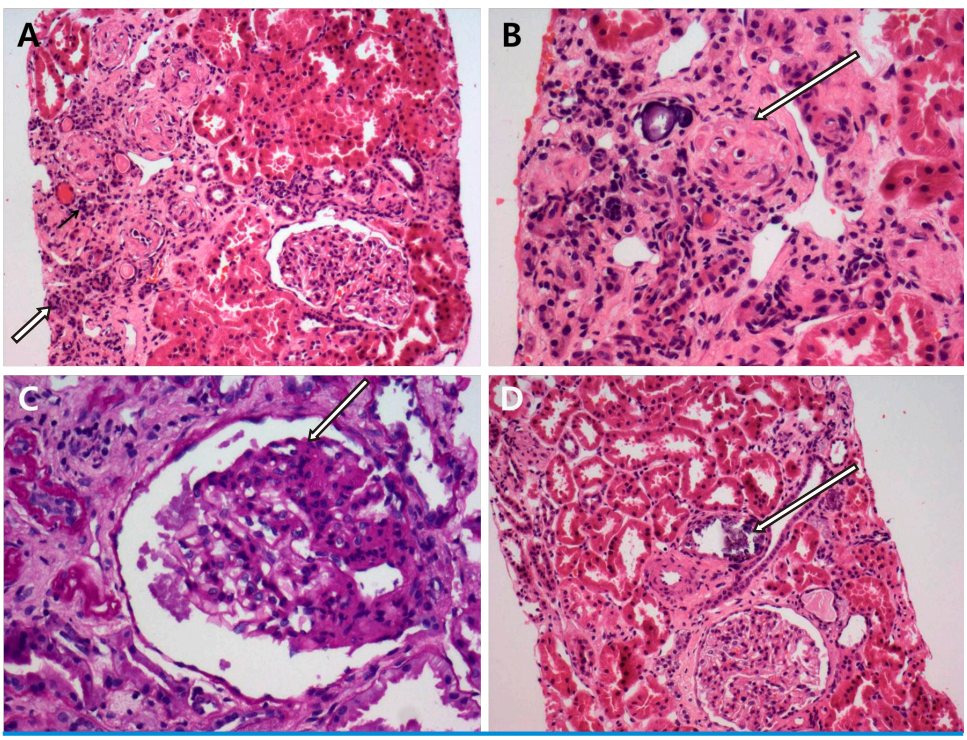

Fig. 1. A portion of dysplastic area is present separated by normal cortical areas. In dysplastic area, immature tubules (arrows) and aggregates of small globally sclerotic glomeruli are shown (H&E, x10, A). In another dysplastic area, metaplastic cartilage (arrow) is shown together with calcification (H&E, x10, B). An enlarged glomerulus showing segmental sclerosis (arrow) (PAS, x20, C). In non-dysplastic areas, focal tubular calcification (arrow) is seen (H&E, x10, D).

result of impaired reabsorption of Na^+ and Cl^- by the intestines. This greatly increases Na^+ and Cl^- reabsorption in the proximal tubule. As a result, the amount of Na^+ and Cl^- that reaches the ThALH and distal nephron decreases, which then in turn negatively affects the passive para-cellular calcium reabsorption[7]. At the same time, dehydration caused by continued diarrhea, as well as hypovolemia, reduces urinary flow, resulting in urine supersaturation, occurrence of crystal precipitation, and progression of nephrocalcinosis. Accordingly, renal biopsy in CLD patients is primarily characterized by calcinosis.

In our patient, however, the main renal injuries included both glomerular sclerosis and renal dysplasia, accompanied by a severely hypertrophic glomerulus, though very little calcinosis was observed. Unlike previous reports, this suggests that a different mechanism in addition to nephrocalcinosis may cause kidney complications in CLD patients. First, the patient's glomerulus showed sclerotic changes. It is unusual to consider this as a difference distinguishing congenital FSGS from CLD, because the patient's clinical pattern and proteinuria were too mild, and because the kidneys continued to function normally. Although no particular treatment was administered to retain kidney function, the patient's serum Cr level was stable, showing less than 1 mg/dL during this period. Furthermore, reductions in urine volume or edema symptoms were not detected. Therefore, the patient's glomerulosclerosis was considered to be a CLD-induced secondary change. In CLD patients, the need for electrolyte reabsorption in kidneys increases because of continued electrolyte loss. This inevitably induces the activation of the renin-angiotensin-aldosterone system (RAAS)[4,5,8]. An activated RAAS increases angiotensin II expression, and the glomerulus can show gradual sclerotic changes as a result[14].

Second, it should be noted that this patient showed characteristics of a dysplastic kidney. As mentioned in the pathology report above, the patient's tissue sample showed metaplastic cartilage, as well as a dysplastic area accompanied by immature tubules. In addition, numerous glomeruli showing global obsolescence were observed. Ours is presumably a case in which kidney malformation occurred due to genetic causes, resulting in interference with normal kidney development and occurrence of global obsolescence. We may hypothesize that focal renal dysplasia in this case may lead to loss of orderly nephrogenesis with decreased functioning nephrons. Thus, the loss of normal nephrons induced hyper-perfusion and hyper-filtration in the remaining glomeruli, resulting in mesangial expansion and compensatory hypertrophy of the glomeruli[15]. Concomitant CLD might also aggravated the tubulointerstitial damage contributing to progression of FSGS.

In conclusion, it is possible that complications in CLD patients can also be caused by an increase in RAAS activity levels, thus renal tissues may exhibit characteristics other than those we generally expect to find in CLD.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgement

This study was supported by a grant (HI12C0014) from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea.

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