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Congenital chloride losing diarrhea
A single center experience in a highly consanguineous population

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Abstract

Congenital chloride losing diarrhea (CCLD) is a rare type of chronic watery diarrhea due to mutations in *SLC26A3* gene leading to defective chloride–bicarbonate exchanges with the resultant loss of chloride and retention of bicarbonate.

We aim to define pediatric Saudi CCLD patients' characteristics to achieve prompt diagnosis, management, follow up with good quality of life, and prevention of complications in these patients.

We carried retrospective data review of demographic, clinical, laboratory, radiographic, and outcome of all pediatric patients fulfilling the criteria of CCLD over 10 years from 2004 to 2014 from a single center in Taif region, Saudi Arabia.

Forty-nine patients fulfilled the criteria of CCLD from 21 families with more than one affected patient in the same family in 90% of them and positive consanguinity in 91% of the cohort. Most patients were born preterm with intrauterine growth restriction and usually neonatal intensive care unit (NICU) admissions with prematurity and its complications. Thirteen patients were discharged without diagnosis of CCLD and 3 were misdiagnosed as intestinal obstruction with unnecessary surgical intervention. Many complications do existed with renal complications being the most common with three patients received renal transplantation.

Prematurity with abdominal distension and stool like urine were the commonest presentation of CCLD in Saudi children. Positive consanguinity and more than one affected sibling are present in most of our cohort.

High index of suspicion by clinicians is a cornerstone for early diagnosis with subsequent favorable outcome.

A multicenter national incidence study of CCLD in KSA and its genetic attributes is recommended. Premarital screening should be implemented specially for consanguineous marriage.

Abbreviations: AGE = acute gastroenteritis, CCLD = congenital chloride losing diarrhea, CKD = chronic kidney disease, Cl = chloride, GFR = glomerular filtration rate, H = hydrogen, HCO3 = bicarbonate, IUGR. = intrauterine growth restriction, K = potassium, KSA = Kingdom of Saudi Arabia, LBW = low birth weight, Na = sodium, NICU = neonatal intensive care unit, *SLC26A3* = solute linked carrier family 26, member 3, U/LRTI = upper and lower respiratory tract infections, U/S = ultrasound, UTI = urinary tract infections.

Keywords: children, congenital chloride losing diarrhea, Saudi Arabia

1. Introduction

Congenital chloride losing diarrhea (CCLD) is a rare autosomal recessively inherited chronic watery diarrhea (OMIM 214700) due to mutations in *SLC26A3* gene (solute linked carrier family 26, member 3; MIM 126650) on chromosome 7q31.[1]

SLC26A3 gene encodes for a coupled chloride (Cl)/bicarbonate (HCO3) exchanger[2] causing Cl absorption and HCO3 secretion in the distal ileum and colon which if absent or defective results in Cl loss in stool with voluminous Cl rich watery diarrhea[3] that begins in utero.[4] Secondarily, the coupled epithelial sodium (Na)/hydrogen (H) transport through the Na/H exchangers (NHE2 and/or NHE3) is defective[5–7] leading to their intestinal loss and acidic stool. Consequently, the renin–angiotensin–aldosterone system is activated with Na reabsorption, potassium (K) excretion and hypokalaemia.[8]

The alkaline feces in other secretory diarrheas exclude the possibility of CCLD.[9–13]

Gamble et al[14] and Darrow[15] were the first to describe this condition in 1945. Since then many cases have been reported with over 30 different mutations in *SLC26A3* gene, without evidence of phenotype–genotype correlation.[16–18]

SLC26A3 gene is expressed in the apical brush border of the intestinal epithelium, in the sweat glands, and in the male reproductive tract.[5,19,20]

More than 250 patients have been reported[21] from various ethnicities with special high prevalence among certain populations with genetic founder effects like Saudi Arabia (KSA). The estimated incidence in KSA is around 1:5500[22] but we believe that it is much higher.

Indeed, most of the available knowledge about this rare disease comes from Finnish investigators who extensively studied their

CCLD population almost from every single aspect of the disease.[1–4,17–21,23] We herein describe our experience with pediatric patients of CCLD who presented to Alhada Armed Forces Hospital, Taif, Saudi Arabia, during 2004 to 2014.

The current study describes this cohort from all possible aspects including patients' demographic characteristics, antenatal and neonatal findings, disease diagnosis, delays in diagnosis, diagnostic pitfalls, disease characteristics including clinical, laboratory and imaging findings, long-term complications, extra-intestinal manifestations of *SLC26A3* gene expression, management protocols and their impact on outcome.

2. Patients and methods

The present study was reviewed and approved by the Institutional Review Board of Alhada Armed Forces Hospital, Taif, KSA. The study protocol involved a retrospective search of the hospital electronic medical records for the past 10 years on all pediatric and adolescent patients <18 years old with a diagnosis containing any of the following key words: metabolic alkalosis, chronic diarrhea, secretory diarrhea, watery diarrhea, chloride diarrhea, chloride losing diarrhea, congenital chloride diarrhea, or CCLD (Fig. 1).

The results of the electronic data base search were then verified through semi-structured interviews with one or both parents conducted by the same physician.

Only patients who were originally from Taif Region and fulfilling the diagnostic criteria of CCLD were included in the study. The diagnostic criteria for CCLD is based on the typical clinical picture of chronic watery diarrhea with high fecal Cl (>90 mmol/L), exceeding the sum of fecal Na and K and a Cl low or free urine in a well hydrated patient with normal serum electrolytes.[1,2]

Supportive data for the diagnosis of CCLD included:

1. fetal ultrasound [U/S] findings of polyhydramnios, hyper-echoic bowel loops, honey comb appearance of the bowel, abdominal distension, and dilated bowel loops with normal peristalsis,
2. neonatal findings of prematurity and low birth weight (LBW),
3. laboratory findings of metabolic alkalosis, hypochloremia, hyponatremia, and hypokalemia.

The following data were collected:

1. Demographic data: gestational age, age at diagnosis, gender
2. Clinical data:
   A. neonatal history: maturity (preterm/full term), birth weight, passage of meconium at birth, abdominal distension, stool characteristics, neonatal intensive care unit (NICU) admission and its cause and duration.
   B. disease characteristics: age at onset of diarrhea, age at definitive diagnosis and presenting complaints.
   C. Developmental data: both physical and mental data were recorded. Heights and weights percentile charts and SD scores were compared with the Saudi reference values. Mental developmental data were also collected.
   D. Family history: consanguinity and other affected family members
   E. Disease complications: enuresis, soiling, failure to thrive, renal affection, dental complication, and repeated hospital admissions (number/year).
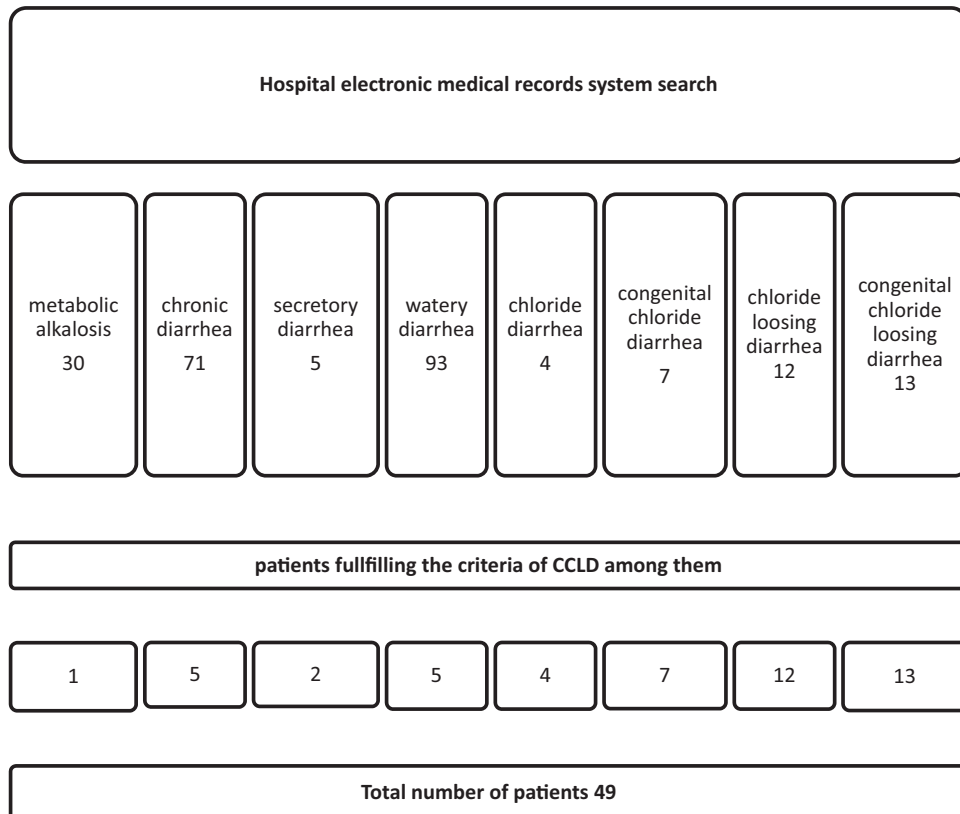

Figure 1. Flow chart of patients' enrollment, selection and pathway.

F. Treatment options: fluid replacement, NaCl supplementation (meq/kg/day), KCl supplementation (meq/kg/day), and use of other management options.

G. Duration and frequency of follow-up

3. Laboratory data:
   - stool electrolytes (Na, K, and Cl), pH
   - urine electrolytes (Na, K, Cl, Calcium, Magnesium, phosphate), protein, pH
   - blood pH
   - serum bicarbonate, electrolytes (Na, K, Cl), uric acid
   - renal functions (urea and creatinine)
   - complete blood picture
   - plasma rennin activity and aldosterone level
   - *SLC26A3* genotype.

4. Imaging data:
   a. Fetal ultrasound done during antenatal follow up looking for: polyhydramnios, abdominal distension, dilated bowel loops, edematous hypoechoic bowel wall, bowel peristalsis, and intrauterine growth restriction (IUGR).
   b. Renal U/S done during follow up visits: renal size, echogenicity, nephrocalcinosis, and others.

5. **Glomerular filtration rate** (GFR) calculation using available laboratory and anthropometric data using Schwartz classic formula (eGFRSch) = {k (height cm)/(serum creatinine mg/dL)}, k is a constant of proportionality.

6. Classifying Grade of Chronic Kidney Disease Stage: according to KDOQI guidelines.[24]

3. Statistical analysis

The collected data had been analyzed using Statistical Package of Social Science (SPSS Inc., Chicago, IL, USA) version 22. Qualitative data were expressed in numbers and percentages while quantitative data were expressed in means and standard deviations.

4. Results

Electronic patients' files analysis revealed 49 patients fulfilling the study inclusion criteria (Fig. 1).

4.1. Demographic characteristics (Table 1)

Forty-nine patients from 21 families, of which 4 families had 4 affected children, another 4 families had 3 affected children, 8 families had 2 affected children and 5 families had one affected child.

Twenty-six (53%) patients were females and 23 were males (47%). All patients were from Taif region, KSA. Positive consanguinity was there in almost 91% of our cohort, most parents were first degree cousins with more than one affected sibling in the family in 90% of them.

4.2. Clinical characteristics (Table 1)

Forty-three patients were born prematurely, and 6 patients were delivered at term. IUGR was observed in all but 2 patients. Meconium was absent in 40 patients and was replaced by watery stool.

Voluminous urine like diarrhea 5.6 ± 3.2 times/day and abdominal distension were constant findings in 80% and 70% of patients respectively at neonatal age.

Table 1

Demographic and clinical characteristics of our cohort of CCLD.

	Finding (number)	Percentage
District of origin	Taif region, KSA (49)	100
Gender	Male (23)	47
	Female (26)	53
Consanguinity	+ve; 44	91
Number of affected siblings in the same family	1 only affected in 5 families	
	2 affected siblings in 8 families	
	3 affected siblings in 4 families	
	4 affected siblings in 4 families	
Gestational age in weeks (WHO classification)	Extreme preterm <28 w (none)	0
	Very preterm 28–32 w (14)	29
	Moderate to late preterm >32 to <37 w (29)	59
	Term ≥37–42 w (6)	12
Birth weight	47 patients were SGA with IUGR	
	2 patients were AGA	
Age at presentation	0–30 days: (47)	96
	1–12 months: (1)	2
	1 year to 18 years old: (1)	2
Age at diagnosis	Fetal: (28)	57
	0–30 days: (5)	10
	1–12 months: (15)	30
	1 year to 18 years old (1)	2
Abdominal distension at birth	+ve: (34)	70
	−ve: (15)	30
Passage of meconium	+ve: (0)	0
	−ve: (40)	82
	NA: (9)	18
Voluminous watery stool like urine	+ve: (39)	80
	−ve: (10)	20

+ve = positive, AGA = appropriate for gestational age, CCLD = congenital chloride loosing diarrhea, IUDR = intrauterine growth retardation, SGA = small for gestational age, NA = data not available, −ve = negative.

Beyond neonatal age, diarrhea persisted with 3.1 ± 2.5 motions/day and abdominal distension markedly improved in all but 3 patients who continued to have severe abdominal distension up to the age of 3 years and developed inguinal hernia.

Patients' ages at diagnosis ranged from fetal/antenatal diagnosis up to 7 months (one patient). One patient was exceptionally diagnosed too late; at the age of 12 years. Both were misdiagnosed as Bartter's syndrome.

Those patients with positive family history were all suspected since fetal life by fetal U/S and definitive diagnosis was confirmed at birth with proper management.

Half of the patients were admitted to NICU due to one or more of the following; prematurity, jaundice, sepsis, respiratory distress, convulsions, or intestinal obstruction. Jaundice and dehydration were present in almost all admitted patients (Table 2). Three patients were admitted to rule-out intestinal obstruction (Table 3).

Thirteen out of the admitted 46 patients were discharged from NICU without being diagnosed as CCLD. All of them were born before 2010.

Although all patients were IUGR during fetal life and were born mostly with LBW, their long-term follow-up revealed reasonable catch up growth for weight, length/height and head circumference by 1 year of age but those with delayed diagnosis had more delayed catch up (Table 4).

Table 2

CCLD patients admitted to NICU and their indications.

Item	Number among the 46 admitted patients	Percentage
Duration of admission	1–12 weeks	
Dehydration at admission	46	(100%)
Electrolytes imbalance at admission	46	100
Prematurity ± SGA	35	76
Hyperbilirubinemia	46	100
Suspected sepsis	7	15
Respiratory distress	6	13
Convulsions	2	4
Suspicion of intestinal obstruction	3	7
Diagnosis of CCLD not achieved before discharge	13	28

CCLD = congenital chloride loosing diarrhea, NICU = neonatal intensive care unit, SGA = small for gestational age.

All patients had normal motor and mental developmental milestones and attended regular school classes with good performance apart from one patient who had psychomotor retardation and needed special school for learning disabilities (Table 4).

Most patients had repeated hospital admissions; 3.1 ± 1.9 times/year; with acute infectious gastroenteritis (AGE), upper and lower respiratory tract infections (U/LRTI), hyperactive airway diseases and urinary tract infections (UTI) especially in the first 2 years of life. Daytime/nocturnal enuresis (26%) and soiling (31%) were common findings during early childhood which improved gradually with increasing age with only minor accidents during night-times and during physical exertion. None had associated chronic inflammatory gastrointestinal diseases (Table 4).

Dental assessment was carried for only 20 patients with enamel pits, opacities or faultiness in 100% of them either isolated or with different combinations while dental caries was present in 75% of patients (Table 4).

Table 3

CCLD patients misdiagnosed as intestinal obstructions.

Patient no	Sex	GA (Ws)	BW (gs)	Age at NICU admission (Ws)	Indication of admission	Duration of admission (Ws)	NICU course	Diagnosis of CCLD reached in NICU before discharge and at what age
1	F	32	1900	At birth	Prematurity Respiratory distress	12	Developed jaundice and sepsis like picture. Persistent abdominal distension→ misdiagnosed as intestinal obstruction→ Operated with colostomy→ with no improvement→ CCLD was suspected → colostomy closed→ discharged home	Yes At 10 Ws
2	M	29	1000	At birth	Prematurity Respiratory distress	10	Developed jaundice and sepsis like picture. Persistent abdominal distension with multiple air-fluid levels→ misdiagnosed as intestinal obstruction→exploratory laparotomy → revealed no obstruction, multiple intestinal biopsies were taken→histopathology came normal. Then at 4 Ws of admission, CCLD was diagnosed.	Yes At 4 Ws
3	F	35	1800	First admission: At birth second admission: at 6 Ws	First admission: Prematurity Respiratory distress second admission:? intestinal obstruction	First admission: 2 second admission: 4	First admission: developed jaundice then discharged. second admission: Operated with colostomy→ with no improvement→ CCLD was suspected → colostomy closed→ discharged home	Not diagnosed in first admission. Diagnosis reached in second admission at the age of 10 weeks.

Table 4

Outcomes and long-term follow up data of the studied cohort.

	Outcome	Number	%
Response to management	•With adequate hydration and electrolytes supplementations all laboratory abnormalities almost normalized.	37	76
	•Poor response was noticed in noncompliant patients who later developed chronic kidney disease	12	24
Favorable outcome with catch-up growth and development centiles for weight, height and head circumference with associated minor morbidity:	1. Diarrhea continued with less number of motions	49	10
	2. Abdominal distension continued beyond 1 year of age	3	6
	3. Inguinal hernia	3	6
	4. Recurrent hospital admissions due to acute gastroenteritis, upper and/or lower respiratory tract infections, hyperactive airway diseases	49	100
	5. Recurrent urinary tract infections	5	10
	6. Enuresis	13	26
	7. Soiling	15	31
	8. Dental enamel pits, opacities, faultiness (20 patients were examined)	In all the 20 examined patients	In 100% of examined patients
	9. Dental caries (20 patients were examined)	15 of the 20 examined patients	In 75% of examined patients.
	10. Hyperuricemia (19 patients were tested)	None of the tested patients	0% of the tested patients
Motor, mental and psychological development	• Normal	48	98
	• Psychomotor retardation	1	2
Major morbidity	1. Chronic inflammatory gastrointestinal diseases	None	0
	2. gastrointestinal malignancies		
	3. Renal involvement	None	0
		12	24
Survival	Mortality	None	0

Renal involvement was found in 12 (24%) patients (Table 4); with varying grades; 8 patients were stage one, one patient was stage 2 and 3 patients were stage 5 chronic kidney disease (CKD). In patients who developed CKD; delayed diagnosis, inadequate salt replacement, or poor compliance were common findings as compared to the remaining study cohort with P value of .047.

Patients with CKD-5 were on peritoneal dialysis and were later transplanted. Two of them were sisters with poor social history with divorced parents and poor parental care, of them one went again into CKD-5 and was transplanted once again.

No deaths due to CCLD were reported in our cohort (Table 4).

4.3. Laboratory findings
4.3.1. Laboratory findings at presentation before starting fluid and electrolytes replacement therapy.
At neonatal period, the first signs of salt depletion were hyponatremia and hypochloremia. Patients with delayed diagnosis had one or more of the following; hypokalemia, metabolic alkalosis, hyperphosphatemia, hypermagnesiemia, high urea, high creatinine, increased plasma rennin activity, and serum aldosterone.

4.3.2. Response to fluid and electrolytes replacement therapy.
With adequate hydration and electrolytes supplementations all laboratory abnormalities almost normalized and all patients had high fecal Cl > 90 mmol/L (105–173) exceeding the sum of fecal Na and K with a low urinary Cl.

4.3.3. Other laboratory findings include.
Uric acid results were available for 19 patients, none of them had hyperuricaemia while sweat Cl testing was available for 18 patients; among them; 7 had levels between 40 and 60 mmol/L and interestingly 3 had cystic fibrosis range (>60 mmol/L).

Genetic testing of *SLC26A3* gene was available for 27 patients who were previously reported by our group on 2014 with the founder mutation c.559G>T (p.G187X) in exon 5 of *SLC26A3* gene.[25]

4.4. Radiological findings

I. Forty patients had their mothers booked for antenatal care with fetal U/S showing polyhydramnios, IUGR and fetal abdominal distension with dilated hypoechoic intestinal loops and normal peristalsis. Honey-coomb appearance of the bowel was looked for in 10 patients and it was positive in them. Data were missing for 9 patients with unbooked mother.

II. Renal U/S showed increased echogenicity with or without nephrocalcinosis and small sized kidneys in 12 patients.

4.5. Management

All patients were kept on life-long Cl supplementation (NaCl and KCl) of about 6 to 8 and 3 to 4 meq/kg/day for those less and more than 3 years old respectively. All parents and older children received education about the necessity of compliance on fluids and electrolytes replacement.

None of our patients received cholestyramine or butyrate. Five patients received proton pump inhibitors; 1 mg/kg/day; with subsequent decrease in the number and amount of diarrheal

motions as reported by the parents but no enough data were available about their stool characteristics and laboratory findings following pantoprazole therapy.

4.6. Follow-up

Patients were closely followed up every 2 and 3 months for those who were less and more than 3 years respectively regarding growth parameters, serum Na, K, Cl, urea, creatinine, blood gases, and urine Cl. Plasma rennin, serum aldosterone and renal ultrasound were followed every 12 months.

5. Discussion

Sporadic single cases of CCLD are being reported from different parts of the world with the main bulk of reported cases from populations with genetic founder mutation like Finland, Poland, Kuwait, and KSA.[1,22] The largest cohort worldwide was from Finland where 46 patients were recruited, among them 36 participated and completed the study.[3]

Some reports were released from KSA[22,25,26] and Kuwait.[27,28] The largest series from KSA was reported from our center and included 27 patients[25] with a total of around 67 reported Saudi patients.[25,26,30–32]

Forty-nine patients fulfilled the inclusion criteria with nearly equal male and female distribution. Up to our knowledge this is the largest cohort in English literature owing to the high incidence of consanguineous marriage in KSA.[22] Positive consanguinity was there in 91% of cases with parents being first degree cousins.

In agreement with other reports,[1,4,27] all patients had watery diarrhea started at birth which often went unnoticed for few days to several months and thought to be urine with consequent delay in diagnosis in some patients specially those born to un-booked mothers. Those with positive family history were diagnosed since fetal life due to the obstetricians' attention to the possibility of disease in other siblings.

As reported by other researchers,[1,4,27] most patients were born preterm with IUGR due to the intrauterine onset of diarrhea which necessitated NICU admissions in 46 patients. Although all admitted patients had dehydration and electrolyte disturbance due to the intrauterine onset of diarrhea, 13 of them were discharged without being diagnosed as CCLD. It seems that the neonatologists attributed dehydration and electrolyte imbalance to prematurity, sepsis or other causes. The proper hydration and electrolytes replacement in NICU prevented the development of metabolic alkalosis that made diagnosis more difficult.

Failure of diagnosis of some patients with CCLD was not noticed beyond 2010 which might be related to better neonatologist awareness about the disease especially with lessons learnt from patients who were undiagnosed or misdiagnosed as other diseases.

As reported before,[1,4,27] neonatal jaundice developed in all patients due to dehydration and prematurity.

Three patients were misdiagnosed as intestinal obstruction due to the absence of the usual meconium, the stool like urine and the severe abdominal distension with unnecessary surgical explorations in all of them; a finding also reported by others.[33]

One of our cohort was extremely delayed in diagnosis until the age of 12 years due to misdiagnosis as Bartter syndrome in another hospital. Interestingly, this patient was thriving well with fairly adjusted serum Na, K, and Cl that was probably attributed to the fact that both Bartter syndrome and CCLD share the same

cornerstone of management which is fluid and electrolytes replacement with different long-term outcomes.

5.1. Long-term outcome

Like other reported cohorts,[1–4,9,22,23,25–29,31,32] our cohort had an overall favorable long term, but some complications do exist especially renal.

5.1.1. Physical and mental growth. In agreement with other[1,3,27]; all patients although born with IUGR; catch up physical and mental growth was achieved during follow up.

5.1.2. Renal complications. Renal complications occurred in 24% of our cohort especially those with delayed diagnosis, less adequate, or poor compliance to salt substitution being in a chronic state of hypovolemia and hypokalemia with renal hypoperfusion and activation of the renin-aldosterone system.[1,3,9]

The incidence of CKD was 28% in the Finnish series with 2 transplanted patients followed by recurrence in both of them.[2] We had 3 transplanted patients with recurrence in one of them.

Despite the protective effect of salt substitution during childhood, the incidence of renal injury in treated CCLD is high. Volume contraction in early life seems to play the most critical role in CCLD-related renal involvement. The normal renal function in one patient with delayed diagnosis in their series, suggests a role for individual compensatory mechanisms.[2] Elrefae[27] and Kagalwalla[25] reported no renal affection in their patients and attributed that to early diagnosis and adequate therapy but it might be also related to shorter duration of follow up.

5.1.3. Urinary tract complications. Enuresis and hospitalizations for UTI occurred in 26% and 10% of patients, respectively. Similar findings were reported in the Finnish population with 8–33% and 36%, respectively.[3] The higher incidence in the Finnish population might be attributed to the inclusion of early series of CCLD patient treated with KCl only before the start of NaCl use.

5.1.4. Gastrointestinal complications. Frequent hospitalizations with dehydration and electrolyte imbalance especially in the first 2 years of life due to AGE and U/LRTI were observed.

AGE may be life-threatening in CCLD patients due to their fragile fluid and electrolytes balance.[3] U/LRTI can cause post tussive vomiting and decrease oral intake.

Soiling was also common in about 31% of our population. Hihnala and coworkers[3] reported soiling in 50% of their group. Soiling occurs because of the watery content of stools.

They also reported an increased risk for intestinal inflammation with three patients diagnosed with unspecified colitis or Crohn's disease. As downregulation of SLC26A3 gene emerges in the inflamed colonic mucosa[34,35] they proposed a link between intestinal inflammation and the primary genetic defect of CCLD. None was diagnosed with chronic intestinal inflammation in our series. This might be related to different age distribution with significant number of adult populations in their series. Long-term follow-up of our population to adult life might be needed to clarify this issue.

Although a slightly increased risk for gastrointestinal malignancies among carriers of SLC26A3 variants has been proposed,[36] no cancers have arisen in the Finnish[3] or Saudi series.

The Finnish group had ten times higher incidence of inguinal hernias in children with CCLD[3,37] suggesting a role for elevated intra-abdominal pressure. We had 3 patients with inguinal hernia in our cohort.

5.1.5. Dental affection.
Among the 20 patients who underwent dental assessment, 100% had enamel hypoplasia and 75% had dental caries. Hihnala group[3] had 25% to 43% incidence of enamel hypoplasia. Interestingly, both hihnala group[3] and Myllärniemi and Holmberg[38] found CCLD protective against dental caries. The incidence of caries in our patients is consistent with the Saudi Arabia caries incidence in children; 70% to 80%; in the latest systematic review released on 2013 by Al Agili[39] which reflects a global country problem and not a CCLD disease problem.

5.1.6. Death.
No deaths from CCLD were reported in our series. Deaths were reported in the early reports from Finnish population,[4] while no deaths were reported after 1972[3] which can be explained by changes in management in early 1970s with the addition of NaCl to KCl the in management protocols as previously described.

5.2. Laboratory findings

In agreement with previous reports,[1–4] our patients had hyponatraemia and hypochloraemia which soon after accompanied by metabolic alkalosis, activation of the renin-angiotensin system and hypokalaemia. If untreated, this metabolic imbalance together with severe dehydration is usually lethal during the first weeks or months of life.[9]

For confirmation of diagnosis of CCLD, we performed stool electrolytes after proper hydration and normal serum electrolytes as volume and salt depletion reduces the amount of diarrhea and may result in a low fecal Cl of even 40 mmol/L.[4,8]

In contrast to Finnish reports,[3] no hyperuricemia was detected in our patients which might be explained by the lower age in our cohort, long-term studies involving adult population are needed to verify that. On the other hand we agreed with the Finnish reports[3,19] in having high sweat chloride; in some of our patients suggesting a minor role for SLC26A3 in the sweat gland. Adding salt substitution during excessive sweating may thus be necessary.[1]

5.3. Genetic testing

Over 30 different SLC26A3 mutations—including the founder mutations of Finland, Poland, and Arabic countries—has been demonstrated to cause CCLD.[18] The founder mutation c.559G>T (p.G187X) in exon 5 of SLC26A3 gene was present in all of the 27 patients in whom genetic testing was performed.

5.4. Imaging findings

I. Fetal U/S: similar to other reports,[28,39–42] fetal U/S revealed polyhydramnios, IUGR, fetal abdominal distension with dilated hypoechoic intestinal loops and honey comb appearance of the bowel in presence of normal peristalsis.

Fetal abdominal distension due to fluid accumulating in their intestine can be considered pathognomonic for CCLD,[41] however dilated bowel loops could be present in other diseases like cystic fibrosis or intestinal obstruction.[27] In the former, the dilated loops are hyperechoic due to the viscosity of meconium[43] while in intestinal obstruction there is associated increased peristalsis in few dilated bowel loops.[44] Although interpretation of these prenatal sonographic features is somewhat subjective, the combination of them strongly supports the diagnosis of CCLD.

II. Renal U/S: In agreement with the Finnish reports,[3] the most prevalent renal involvements were increased echogenicity, nephrocalcinosis, and small sized kidneys. A prospective cohort study on renal complications in Saudi CCLD is now running in our center for more accurate precise data on renal affection.

5.5. Management

Since the intestinal defect in CCLD cannot be corrected, management is logically to be life-long with both NaCl and KCl solutions. CCLD in a newborn is a medical emergency.[4,9] Early diagnosis and adequate replacement therapy are the cornerstone for normal physical growth and mental development.[4,21,45]

The life-saving therapy for CCLD with salt substitution was introduced in Finland in the late 1960s.[1,3] Thereafter, it has been used worldwide.[4,9] The optimal dosage of Cl ranges from 6 to 8 mmol/kg/day in infants and from 3 to 4 mmol/kg/day in older patients.[3,8,9]

It is to be noted that higher than optimal dosage of salt substitution increases the amount of diarrhea by osmotic mechanisms.[17] On the other hand, a major sign of inadequate salt substitution is the decreased amount of diarrhea.[8] Salt substitution increases intestinal absorption by unspecified mechanisms and inhibits development of hypochloremic and hypokalemic metabolic alkalosis.[1] The rationale behind this therapy is the normal jejunal absorption of these electrolytes in CCLD patients.[27]

Despite therapy, the defective SLC26A3-mediated anion transport remains in the intestine and the diarrhea is persistent. Although the relative amount of stools decreases with age, intestinal loss of electrolytes, and especially that of Cl is continuous. If the dosage of salt substitution is insufficient, hypochloremia and active reabsorption of Cl both in the distal colon and in the distal nephron result in Cl free urine.[1]

Accordingly, adequate excretion of Cl into the urine, in addition to normal electrolyte and acid-base status, confirms the sufficiency of salt substitution.[3,4,9]

All admitted patients were started on IV hydration and electrolytes therapy until normalization of serum levels followed by oral therapy. The oral Cl dose was titrated based on adequacy of urinary Cl excretion indicating normal extracellular fluid volume[1] which should be 10 to 30 mmol/L for those 3 to 7 years and at least 30 to 50 mmol/L in older children.[9,46]

Some authors tried cholestyramine[3,47,48] with transient improvement. Others tried butyrate with promising results in some populations.[49–51] None of our patients was tried on any of them due to unavailability in our center.

Proton pump inhibitors showed good results in some reports[52–54] while others showed no efficacy.[17,50] Five patients in our cohort were on pantoprazole therapy with promising results. A prospective cohort study on pantoprazole therapy was carried for 1 year in our center with promising results (data under publication).

5.6. Frequency of follow up

We agreed with other reports[1–4,27] on the need for strict follow up. We carried more frequent follow up for those <3 years; 6 times/year; to ensure strict adherence to replacement therapy and provide continuous education to parents who were highly resistant to accept the fact that their children has lifelong disease.

6. Limitations

Being a retrospective study, available data were only analyzed without any control on the settings of the different aspects studies. Some elements were studied in only part of the population.

"WHAT IS ALREADY KNOWN ON THIS TOPIC"

1. CCLD have been investigated in Finnish population from almost all aspects.
2. Little is known about CCLD in Arab population in general and Saudi Arabia in particular with the largest cohort published included only 12 patients.

"WHAT THIS STUDY ADDS" –

This study thoroughly investigated Saudi CCLD patients from all aspects.

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7. Conclusions and recommendations

This single center study included 49 children with CCLD diagnosed in 10 years, warrants an incidence study of CCLD in KSA. Complications of CCLD are potentially preventable with early diagnosis and management. Neonatal screening for CCLD in KSA might prove to be cost-effective as complications of CCLD are preventable. This high burden of disease in KSA necessitates mass education of public about the disease along with discouraging consanguineous marriage.

High index of suspicion by clinicians especially obstetricians and neonatologists is needed and education programs for health care workers should be implemented.

A multidisciplinary team should follow CCLD patients including pediatric/adult gastroenterologist, nephrologist, dentist, dietitian, nutritionist, health educator, and social worker is highly recommended.

Saudi patients are receiving the standard international care of CCLD but still a Saudi multicenter study involving both pediatric and adult populations is warranted for better characterization of our population and release of national guidelines.

Author contributions

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