

Congenital Chloride Diarrhoea: First Time Diagnosis in Bangladesh and its Management Difficulties

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Abstract

Congenital Chloride Diarrhoea (CCD) is a form of autosomal recessive disorder which is presented by persistent chloride rich watery diarrhea from birth. Diagnosis of CCD is simple but it needs early prediction and clinical and laboratory evaluation. It can be tentatively made from the typical history of polyhydramnios in antenatal period, prematurity, and watery diarrhea from the beginning and then confirmed by the high fecal concentration of Cl⁻. Serum electrolyte and pH changes are not reliable diagnostic criteria. Without early intervention most of the children will die in infancy, rest will achieve failure to thrive, and psychomotor developmental delay. Although congenital chloride diarrhoea has been reported worldwide, but in Bangladesh, we have no reported cases. Here we have discussed two cases of CCD with their diagnostic and management outcome and also discuss about captopril and its effectiveness. Early diagnosis and treatment are essential for normal growth, development, and prevention of other severe complications of congenital chloride diarrhea.

Introduction

Congenital Chloride Diarrhea (CCD) is an inherited disorder of intestinal electrolyte transport, which is transmitted through autosomal recessive manner due to the mutations of solute carrier family 26 members [1]. This gene is located close to the cystic fibrosis transmembrane conductance regulator gene [1]. Its Prevalence is more in Finland, Saudi Arabia, Kuwait, and Poland. Consanguinity of marriages is one of the main factors for high incidence like Saudi Arabia and Kuwait such as 1 in 5000 [2] but in Bangladesh, CCD incidence is not known and there was no previously any reported cases. Diarrhea starts at fetal life which causes polyhydramnios and in most of the cases finally causes premature delivery [3] early diagnosis in infancy is essential for saving life and also prevent the mental and psychomotor impairment and the chronic contraction of the intravascular space leading to renal dysfunction and gout [3]. The loss of the SLC26A₃ is the basic defect-that results in defective intestinal absorption of Cl⁻ and secretion of HCO₃⁻. Finally the coupled epithelial Na⁺/H⁺ transport through the Na⁺/H⁺ exchangers (NHE₂ and/or NHE₃) is defective which causes intestinal loss of both NaCl and fluid, and ultimately develop Cl⁻-rich watery diarrhoea. If untreated, dehydration causes activation of the renin-angiotensin system [4] and finally, Hypochloreaemia with hypokalaemic metabolic alkalosis is the main laboratory findings. So, early diagnosis is essential for the beneficial of the patient.

Case Discussion

Case-1

An eight month twenty-two days old male baby got admission with the history of chronic watery diarrhea from birth and poor weight gain. His medical data revealed parental consanguinity and a history of Polyhydramnios and premature birth (at 35 weeks of gestation) and his birth weight was 2.3 kg. He had been hospitalized for several times due to diarrhea and its complications. One of his brothers was died at the age of 7 month with same problem but his two sisters were all right. He was partially breastfed. His stool was watery in nature, frequency 12-15 times per day, not associated with visible blood and straining. Sometimes the watery content of diarrhea had been confused with that of urine. Clinical assessment revealed patient was less active with some signs of dehydration. Anthropometric measures were weight 5.83 kg (-3.75 SD below mean for age) and blood pressure was normal for his age and abdomen was soft, mildly distended but no organomegally. We did not advice any Genetic testing, as because it was not available

in Bangladesh. Serum electrolyte report showed hypochloreaemia, metabolic alkalosis, hyponatremia and hypokalemia (Table 1). With increased levels of plasma renin but serum aldosterone [203 pg/ml (normal: 25-315)] level was normal. Sweat chloride level was also normal. Stool microscopy shows only reducing substances, and stool culture for *V. cholera salmonella*, *Shigella* and *Campylobacter* showed no growth. Finally we did stool electrolyte and it shows fecal chloride content >90 mmol/L and Fecal chloride >fecal (Na⁺ K) and exclusion of other diseases. The baby required a high dose of sodium chloride and potassium chloride (4 mmol/kg/day) to normalize his potassium, chloride, and sodium levels. He was referred to a dietician to be given a high-calorie formula and the Patient was then discharged on oral salt supplementation with syp potassium chloride and syp Omeprazole. Watery portion of stool was reducing little bit but not completely and the other physical condition was improving. The child afterwards had multiple admissions due to breakthrough of illness. Electrolyte imbalances were corrected with both oral and intravenous fluid and he was gradually gaining weight. Currently under follow-up at 42 month of age showed good catch-up growth. The developmental milestones were appropriate for his age. The boy was referred to ophthalmology; ENT and pediatric neurology subspecialty for evaluation and it was normal. There were no speech delay and no hyperactivity behavior.

Case-2

An eleven month twenty-two days old partially breast-feed female baby, got admission with the history of polyhydramnios at intrauterine life, and from a healthy consanguineous parent at 35 weeks of gestation and her birth weight was 2.1 kg. Her admission complains was diarrhoea from birth with occasional vomiting and failure to thrive. Stool was watery in nature, frequency 8 to 10 times

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	Sodium	Chloride	Potassium	TCO2	Glucose	Calcium	Magnesium	Creatinine
Normal Value	135-45 mmol/l	97-106 mmol/l	3.5-5.3 mmol/l	18.0-24.0 (child) mmol/l	3.3-5.6 mmol/l	2.1-2.6 mmol/l	0.65-1.05 mmol/l	18-35 umol/l
1 st test	129.5	64.7	1.95	51.4	5.5	2.61	0.68	19.8
2 nd test	117.6	58			4.8	2.46	0.99	22.8
3 rd test	112.5	56	1.99	53.8	6.3			21.2
4 th test	126.4	72	3.01	50.4	5.3	2.62	0.70	18.7
5 th test	132	77	3.1	35	5.2	2.78	0.89	15.6

Table 1: Results of serum electrolyte.

	Random Urine Electrolytes				Random stool electrolytes			
	Sodium	Chloride	Potassium	Calcium/creatinine ratio	Magnesium	Sodium	Chloride	Potassium
Normal	15-20 meq/l	15-20 meq/l	15-20 meq/l	<0.6	0.6-0.9 mmol/l	50-60 mmol/l	6-17 meq/l	NA
Case-1	10	15	30.8	0.22	Not done	71	119.7	33
Case-2	16	12	18.8	Not done	Not done	82.9	126.6	30.2

Table 2: Results for urine and stool electrolyte.

	Sodium	Chloride	Potassium	TCO2	Glucose	Creatinine
Normal Value	135-45 mmol/l	97-106 mmol/l	3.5-5.3 mmol/l	18.0-24.0 mmol/l	3.3-5.6 mmol/l	18-35 umol/l
1 st test (After 5 days getting KCL with ORS occasional I/V1)	137	82.45	2.52	31.79	5.5	23.4
2 nd test (After 3 days stop KCL with ORS)	130.2	74.3	2.94	41.6	5.8	29.2
3 rd test (ORS)	126.2	59.8	2.36	58.8	4.5	47.4
4 th test (ORS)	134.95	68.73	2.87	50.18	5.2	33.3
5 th test (After I/v correction 1 (No ORS)	140.77	79.13	3.96	43	4.6	45
6 th test (Syp KCL & Nacl) (with ORS+above I/V)	137.7	104.4	4.99	26.0	5.2	15.0
After adding Captopril with (Syp KCL & Nacl with ORS)	137.47	105.94	5.65	21.32	4.8	15.86
Only Captopril (with ORS after 1 day of strated it, no KCL and no NaCl)	135.3	95.4	3.87	27.1	5.2	18
Only Captopril After 7 days (No KCL and no NaCl)	137.09	92.34	3.41	30.98	4.8	15
1 st follow up after discharge (Captopril with ½ TSF of KCL twice a day)	136.6	91.91	3.14	26.7	4.6	18.5
2 nd follow up (Captopril with 3/4 th TSF of KCL thrice a day)	135.2	76.5	3.44	28.4	5.1	21.4

Table 3: Results of serum electrolyte.

per day, not associated with blood and undigested food particle. There was a history of hospitalization at her neonatal period due to sepsis and Hyperbillirubinaemia for 1 month and also had several episodes of hospitalization before coming to our hospital for diarrhoea but her diarrhoea was not improving. She did not have any history of cyanosis or heart disease. During admission patient was sick looking and less active with some signs of dehydration. Patient weight was 3.8 kg Height 61 cm pulse-110/min with BP 90/50 mmHg, T-36.8c, Pulse 128/min, R/R-38/min, Spo2-99%, no chest in drawing, lungs-clear, Abdomen was soft, mildly distended, Bowel sound was normal. Her developmental milestones (motor) (neck control yet not established) were slightly delayed. Initially we manage the case as chronic diarrhoea with some d/h with severe acute malnutrition. For less active we differentially thought electrolyte imbalance and sepsis. We have done some investigations like CBC, Serum electrolyte and Creatinine, Blood for C/s, stool R/M/e and c/s with Urine R/M/E with Chest X-Ray. This electrolyte report (Tables 2 and 3) showed persistent hypochloramic hypokalemia with alkalosis and for that reason we differentially thought-gastric outlet obstruction, Cystic Fibrosis, Bartter syndrome and congenital chloride Diarrhoea. Sweat chloride level was normal. Stool routine microscopy was normal;Urinary electrolytes were Na⁺: 16 mmol/L (normal: 54-150), K⁺: 24.52 mmol/L (normal: 20-80), and Cl⁻:12 mmol/L (normal: 110-250). Tissue transglutaminase Immunoglobulin (TtG-IgA) and IgG antibodies were negative, Plasma

T.Protein-86.47 g/L (normal range 64.0-82.0) Albumin-48.97 g/L (34.0-50.0) Globulin 37.5 g/L (23.0-35.0) A: G Ratio-1.31 (1.10-1.80). Stool electrolyte report shows-Chloride (Stool) 126.6 mmol/L, Potassium (Stool)-30.9 mmol/L, Sodium (Stool)-82.9 mmol/L. The diagnosis of CCD was confirmed on the basis of the results of stool electrolyte of faecal chloride content >90 mmol/L and fecal chloride >fecal (Na⁺ K) and exclusion of other diseases. Genetic testing was not done, as it was not available in Bangladesh. Urine and stool culture shows no growth. We started oral NaCl and KCl Supplementation with commercially available oral formulation of omeprazole. Oral butyrate was not used as it is not available in Bangladesh. After 15 days of hospitalization, patient developed fever and respiratory distress. Her respiratory rate (64/min) with increase heart rate (175/min) and X-ray was suggestive of pulmonary oedema. For the suspicion of Hospital acquired infection we initially treated the patient with inj Ceftazidime and inj amikacin but there was no improvement so switched to Inj. Imipenem but when we got the blood c/s report it showed Acinetobacter species and it was sensitive to Polymyxin B. we started inj polymyxine B and at that time patient also developed changing murmur and we suspected the case as infective endocarditis probably due to septicemia and continuous intravenous fluid infusion so, we did Echocardiography and it shows mild coarctation of aorta, with mild mitral regurgitation grade 1 and mild pulmonary Hypertension with normal EF-70% . We added captopril for Heart failure and wait for adding digoxin for next step.

After adding captopril, surprisingly stool output was significantly reduced and serum potassium was increased. So we reduced the dose of syrup KCl and NaCl and only continued captopril, patient condition was improving, stool output and consistency was also improving, patient electrolyte profile was also normal for last 6 months, and last echocardiography showed mild TR. Trivial MR, good biventricular function. LVEF-69% FS (%) -37 LVID-15 LVID-24 PPG-20 mmHg, inter atrial septum and inter ventricular septum was intact and there was no PDA or coarctation of aorta. No vegetation and intracardiac mass and finally the cardiac anatomy showed normal findings. Patient is gradually gaining weight from 3.8 kg to 6.4 kg and now, her head control is completely normal.

Discussion

Congenital Chloride Diarrhea (CCD) is a rare hereditary disease, with a prenatal onset, secondary to a deficit in the intestinal chloride transport. It is more common in Finland, Poland, and Arab countries. Diagnosis at neonatal period is often delayed in low-incidence regions like Bangladesh (these two cases are the first reported cases of CCD in Bangladesh) due to lack of knowledge and experience. Here we have discussed two cases. Both of the babies had consanguinity of marriage between their parents, polyhydramnios at intrauterine life, watery diarrhea from birth and failure to thrive and laboratory findings showed persistent hypochloramic hypokalemia with alkalosis. We treated the first baby with omeprazole and KCl, NaCl substitution and adding green banana in his regular diet. Though the diarrhoeal frequency was reduced but not resolved and watery portion was still present and follow up at 42-month showed, his mental and motor development was completely all right. The cause of exacerbation is primarily due to any infection, other associated disease or any other cause of diarrhoeal episodes or vice versa. The first striking presentation of both patients was hypochloremic hypokalemic alkalosis and history of chronic diarrhoea from birth with polyhydramnios. Sometimes it is difficult to correct electrolyte imbalance and dehydration by oral replacement and needs intravenous correction but the main problem is hospital-acquired infection due to prolonged hospitalization. Our second patient developed hospital-acquired infection by acinobacter and finally diagnosed as a case of infective endocarditis with heart failure. For the management of heart failure we started captopril but surprisingly after starting captopril patients' watery portion of diarrhoea was significantly reduced and stool output was reduced from 400 to 600 ml/day watery stool to 20 to 90 ml/day semisolid stool and reduced the need of potassium and NaCl supplementation. Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyl dipeptide carboxy hydrolase. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss. So it can be an option for reduction of diarrhoea and need regular management. Rice based ORS and diet was better to tolerate. Congenital Chloride-Losing Diarrhoea (CCD) is the best-described congenital defect of large intestinal transport and characterized by watery diarrhoea with high levels of stool chloride, which exceed the sum of stool sodium (Na) and potassium (K), and low stool bicarbonate (HCO_3^-) concentrations and pH. Since the first reports of CCD in 1945 [2] the defect in anion exchange leading to high stool chloride concentrations may theoretically be due to either failure of chloride absorption or to active secretion of chloride into the intestine. The alkalosis probably develops partly through an associated increase in H^+ excretion and partly through an absence of HCO_3^- secretion in the ileum and colon. So

metabolic alkalosis can be divided into two ways - 1) chloride-responsive alkalosis (urine chloride <20 mEq/L) and 2) chloride-resistant alkalosis (urine chloride >20 mEq/L), that is why we have done urinary electrolyte and it shows urinary chloride is 12 mmol/L (<20 mmol/L) so it is chloride-responsive alkalosis and causes of chloride-responsive alkalosis are loss of gastric secretions. Like vomiting, NG suction and loss of colonic secretions - congenital chloridorrhea, villous adenoma, diuretics use, cystic fibrosis. If chloride-responsive alkalosis occurs with volume depletion, treat the alkalosis with an intravenous infusion of isotonic sodium chloride solution. Because this type of alkalosis is usually associated with hypokalemia, also use potassium chloride to correct the hypokalemia. So we corrected alkalosis and hypokalemia with normal saline and 5% dextrose and 20 mmol/L inj potassium chloride and it was finally corrected (2nd patient in Table 3). Patient got captopril for heart failure and it increases potassium and improves alkalosis as because captopril inhibits conversion of angiotensin I to angiotensin II which is a potent vasoconstrictor, resulting in lower aldosterone secretion [4]. Biochemical abnormalities in CCD are similar to those in pseudo-Bartter syndrome apart from urinary chloride content, which is low in untreated CCD but high in all forms of Bartter syndrome. In case of metabolic alkalosis Bartter's syndrome and cystic fibrosis is one of the differential diagnosis. Infants with cystic fibrosis can also present with episodes of hyponatremic, hypochloremic dehydration with metabolic alkalosis, which are also biochemical hallmarks of the pseudo-Bartter syndrome [5]. The sweat chloride level was normal in both patients and we should be aware that increased concentrations of sweat Cl⁻ were reported in 12% of CCD patients [5]. Differentiation from Bartter's syndrome (Especially in our first case) and Gitelman's syndromes were less likely in our patient as it was associated with diarrhoea. Pseudo-Bartter syndrome, such as chronic diuretic use, chronic administration of a chloride-deficient diet, cyclic vomiting, and abuse of laxatives, were absent in our patient. We should obtain a correct urinary specimen by placing of urinary bags. Other causes of congenital watery diarrhoea, such as congenital glucose-galactose malabsorption and congenital sodium diarrhoea, cause metabolic acidosis instead of metabolic alkalosis [6]. An increase in stool volume, mostly accompanied by respiratory infections [6]. We have also excluded celiac disease by negative tissue transglutaminase antibodies. One of the late manifestations of CCD is growth retardation [6] however; other factors could contribute to stunted growth in this patient, e.g., repeated readmission, which interferes with wellbeing and appetite. Urinary tract infections were frequent in our patient but rare with our present mode of treatment. In the long run, incidence of renal impairment is high, and sometimes it is difficult to prevent it with proper salt and fluid substitution therapy. The main focus point of treatment of congenital chloride diarrhoea is (i) life-long salt and potassium chloride substitution (ii) early treatment of the acute dehydration and hypokalaemia during gastroenteritis or other co-infections; and (iii) early recognition and treatment of other complications of the disease, such as intestinal inflammation, renal impairment. Many therapeutic attempts have demonstrated to be ineffective in reducing the severity of the disease and its long time complications. Replacement therapy with per oral NaCl and KCl substitution has been shown to ensure normal growth and development in children and partially prevent complications, but it did not reduce the diarrhoea. Over-substitution must be avoided because it may even increase diarrhoea by an osmotic mechanism [7]. Regular ORS omeprazole did not completely stop the watery portion of diarrhoea but reduced significantly. Again butyrate and cholestyramine can be used as diarrhoea-reducing therapies. But it does not completely reduce the watery portion of stool. But in our second patient, when we started captopril, it significantly reduced

watery portion of stool and almost resolve for long time and reduce the dose of potassium chloride supplementation. Acute exacerbations of electrolyte imbalance remained labile and disturbed even by slight infections. The patient will learn to live with their diarrhea and to make an adequate social adjustment.

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