Journal of Korean Medical Science
Vol.3, No.3, P123-129, September 1988

Congenital Chloridorrhea in Korean Infants

Young Don Lee, M.D., Hong Jin Lee, M.D., and Hyung Ro Moon, M.D.

Department of Pediatrics, College of Medicine, Seoul National University, Seoul Korea.

The present paper describes two Korean male infants, 1. 16year old and newly born neonate from two families who were diagnosed and managed for one of very rare inborn errors of metabolism, congenital chloridorrhea (Darrow-Gamble syndrome).

The diagnosis was suggested by one of the authors (HRM) from the unusual combination of metabolic alkalosis with severe gastrointestinal disorder presenting with chronic, profuse watery diarrhea in the newborn period in the first patient; and the maternal polyhydramnios, the appearance of dilated fetal bowel loops on prenatal ultrasonography and profuse watery diarrhea beginning at birth without passage of meconium in the second patient.

The diagnosis was confirmed in both patients by examination of the stool chloride concentration which revealed extremely high exceeding the sum of sodium and potassium concentrations. Serum electrolytes and arterial blood gas analyses revealed hyponatremia, hypokalemia and hypochloremia with elevated bicarbonate. With replacement of fluid and electrolyte deficit and adequate dietary supplements of potassium and chloride, both patients remained well although the character of the stools waxed and waned.

This is the first reported case of congenital chloridorrhea in korean population.

Key Words: *Congenital chloridorrhea, hypochloremia, hypokalemia, metabolic alkalosis, polyhydramnios.*

INTRODUCTION

Specific intestinal absorption defects were known only for Zn^{++} (acrodermatitis enteropathica). Cu^{++} (Menke's kinky hair disease), Na^{+} (congenital scdium diarrhea), and Cl^{-} (congenital chloridorrhea) (Holmberg & Perheentupa, 1985).

In 1945 Gamble and Darrow both described a child who had persistent watery diarrhea, high fecal concentration of Cl^{-}, hypochloremia, hypokalemia and metabolic alkalosis and they diagnosed the illness as 'congenital alkalosis with diarrhea'. Since then about 60 cases have been reported in the literatures all over the world of which nearly half were reported in Finland (Holmberg & Perheentupa, 1985). But in other countries only a few cases were reported (Holmberg et al., 1977 a) and in Asia only one case was described in the literature (Yanagisawa et al., 1968).

Congenital chloridorrhea is inherited as an autosomal recessive trait, which implies an abnormality in a single gene pair, a single protein, and a single cell function (Norio 1971). Launiala (1968) showed that the intestinal defect is located in the distal ileum and colon. Studies of the ileum (Bieberdorf 1972, Pearson 1973) and colon (Pearson 1973, Holmberg 1975) have shown, more over, that this defect is impaired active Cl^{-} absorption resulting from an absence or impairment of the Cl^{-}/HCO_3^{-} active exchange mechanism in these segments of intestine. But passive exchange mechanism was proved to be normal. Cl^{-} is lost in the stool and osmotic diarrhea develops. The absence

Address for Correspondence: *The department of Pediatrics College of Medicine. Seoul National University. 28, Yeon Keon Dong Jongno-Gu, Seoul, Korea.*

This study is in part supported by Clinical Research Grant (1983).

of HCO_3^- causes the intestinal content to become acid which in turn restricts the absorption of Na^+ (Rudolph, 1987).

CASE REPORTS

Case 1

A 1. 16year old boy was admitted for the first time to the Dept. of Pediatrics of Seoul National University Children's Hospital because of chronic diarrhea and failure to thrive on April 8, 1988. He was born as a preterm baby (gestational period; 36 weeks) with slightly distended abdomen. The birth weight was 3.1 kg and large for gestational age. There was a history of maternal polyhydramnios. After birth he did not pass the meconium. On the 6th day of his age icteric skin color and watery diarrhea were detected by his mother and he was brought to an university hospital and managed for 'neonatal hyperbilirubinemia' (maximum serum bilirubin level; 19.7mg/dl), but neither specific diagnosis nor treatment was given for the diarrhea. After discharge from the hospital his diarrhea continued wax and wane. When aggravated his stool became watery as if urine with frequency up to twenty times a day, when improved his stool became formed in soft consistency with frequency of three to four times a day. He was admitted to three more hospitals for four more times for evaluation and treatment of irritability and diarrhea but without specific diagnosis he was placed on diet consisting of soy bean milk and powder mixture of rice, sesame, chestnut and dried anchovy.

About three weeks prior to admission he developed nasal stuffiness and rhinorrhea and six days prior to admission his diarrhea became aggravated to watery stool with frequency of twenty times a day.

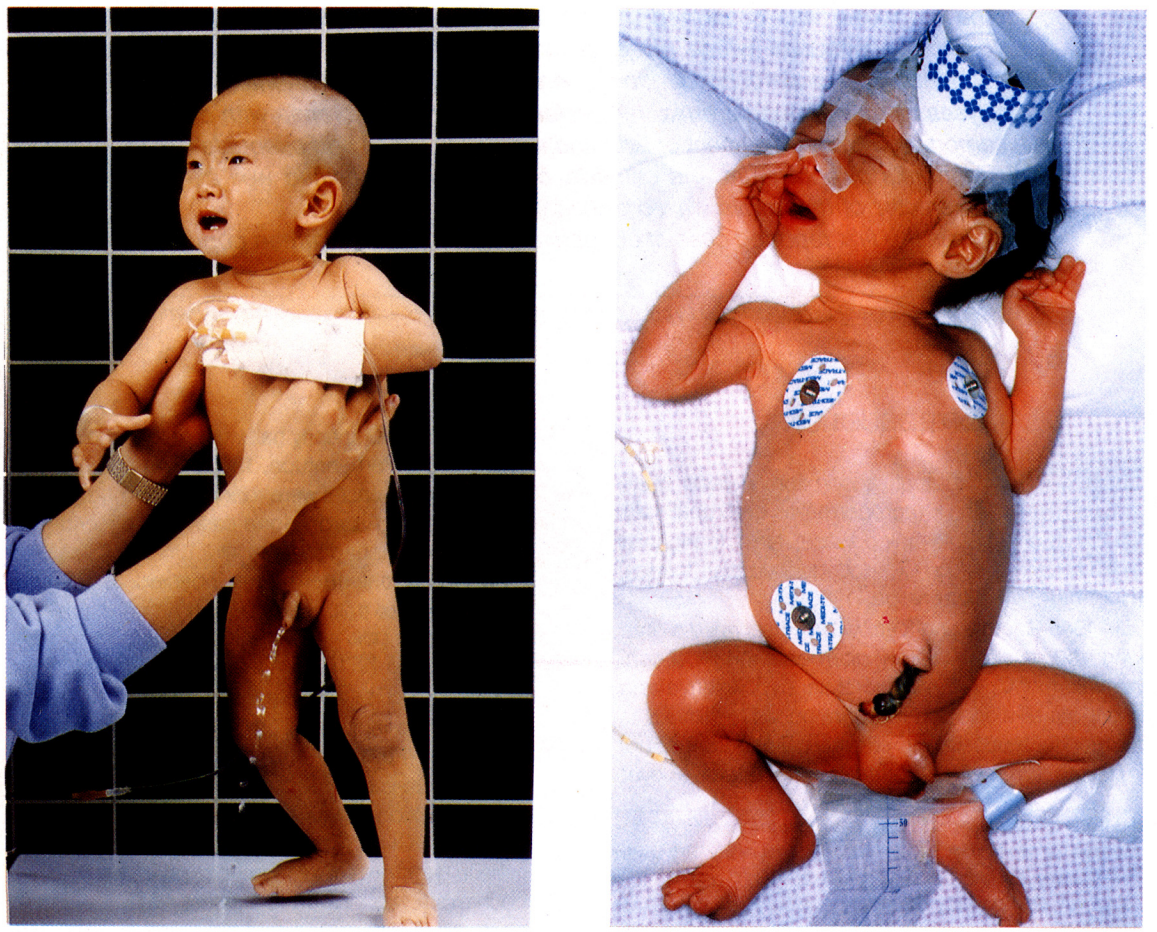

Fig. 1. General appearance of patient 1 (left) and patient 2 (right). Note marked abdominal distension and visible bowel loops in patient 2.

Physical examination on admission revealed a severely emaciated and alert patient with mildly distended abdomen (Fig.1.). The temperature was 36.5°C, the pulse 80 per minute and the respiration 18 per minute. The blood pressure was 80/40 mmHg. The weight was 7.65kg (below 3 percentile) and the height 76cm (10-20 percentile).

The urine was colorless, PH 6.0, specific gravity 1.015. The urinary sediment was normal. The hematocrit was 40.2 percent; the white cell count was 12,800 with 8 percent stab formed neutrophils, 61 percent segmented neutrophils, 28 percent lymphocytes, 2 percent monocytes and 1 percent eosinophils. The arterial blood gas analysis showed the PH 7.65, $PaCO_2$ 34 mm Hg, PaO_2 120 mmHg and bicarbonate 38 mEq/l. The sodium was 130 mEq, the potassium 2.6 mEq and the chloride 75 mEq per liter. Spot urine electrolyte analysis showed the sodium 23 mEq, the potassium 50 mEq and the chloride 14 mEq per liter. The stool electrolyte analysis showed the sodium 124 mEq, the potassium 27 mEq and the chloride 138 mEq per liter. The stool pH was 6.0. The bone age was six months. A small bowel series showed mild mucosal thickening in the proximal intestine. The colon study and the X-ray film of the chest were normal. The stool examination showed no helminth ova, no protozoa and no occult blood. The stool culture showed no growth. The serological studies including VDRL, CRP and HBsAg/Ab were normal.

After admission, under the diagnosis of congenital chloridorrhea, electrolyte replacement was done with rapid normalization of serum electrolytes and acid base status (Table 1). From the 5th hospital day the stool became soft in consistency with frequency of five times a day.

Case 2

A new born male infant was transferred from the delivery room to the neonatal intensive care unit of Seoul National University Children's Hospital under the suspicion of ileal atresia' on May 24, 1988 due to the findings of maternal polyhydramnios and dilated fetal bowel loops on the prenatal ultrasonography (Fig.3). The gestational period was 38^{+6} weeks. The birth weight was 2.42kg. Apgar scores at 1 and 5 minutes were 9 and 10, respectively. On physical examination the head, neck, chest and extremities were normal but the abdomen was markedly dilated with visible bowel movement (Fig.1). Ascites was absent. The liver, spleen and kidneys or other mass was impalpable. Immediately after the birth yellow watery diarrhea was detected by a nurse (Fig.2). However, meconium was not passed. Arterial blood gas analysis showed the pH 7.46, $PaCO_2$ 32 mmHg, PaO_2 77 mmHg and bicarbonate 23 mEq/l. The serum electrolyte analysis showed that the sodium was 135 mEq, the potassium 4.8 mEq and

Table 1. Acid-base status and electrolyte concentrations of serum and stool of patient 1. Electrolyte replacement was started on the first hospital day.

Hospital Day	ABGA pH-$PaCO_2$ PaO_2-HCO_3^-	Serum Na-K-Cl mEq/l	Stool Na-K-Cl mEq/l	Stool-Chara/ Freq.
1	7.65-34-120-38	130-2.6- 75	124-27-138	Watery/20/day.
2	7.54-36-110-31	134-3.7- 94		Watery/15/day.
3	7.40-42- 72-26	140-5.0-114		Watery/15/day.
4	7.40-40-116-23	141-5.4-112		Soft/4 /day.

Table 2. Acid-base status and electrolyte concentrations of serum and stool of patient 2. Electrolyte substitution with 0.7% NaCl and 0.3% KCl was started on the third day of his age.

Age	ABGA pH-$PaCO_2$ PaO_2-HCO_3^-	Serum Na-K-Cl mEq/l	Stool Na-K-Cl mEq/l	Stool-Chara/ Freg.
1 day	7.46-32- 77-23	135-4.8-106	136-5.6-143	Watery/15/day.
3 day	7.50-24- 90-19	121-4.4- 87	158-13.2-169	Watery/15/day.
5 day	7.41-31- 72-19	143-4.8-118		Watery/10/day.
7 day	7.33-26-113-14	146-5.1-116		Soft/5/day.
14 day	7.41-38-95-20	134-5.4-106		Watery/15/day.

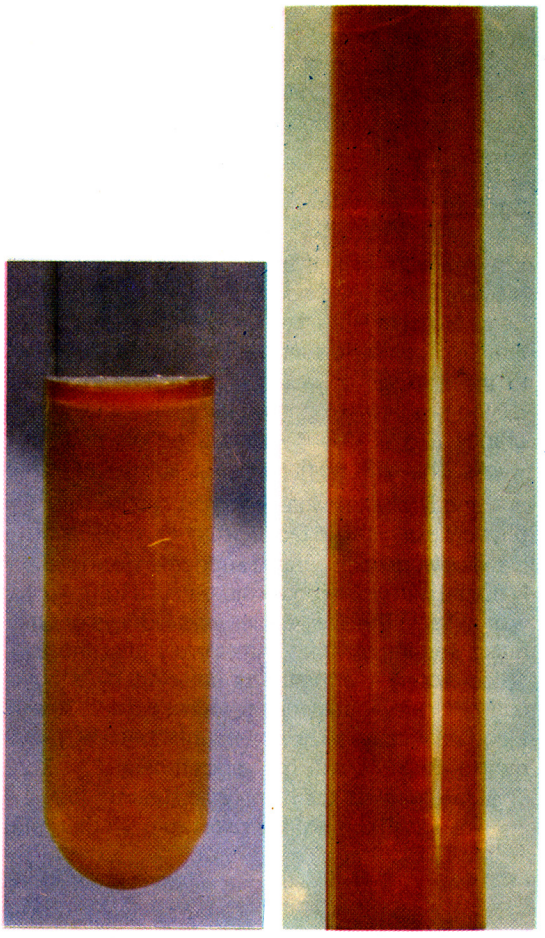

Fig. 2. The characteristic urine-like appearance of stools of patient 1 (left) and patient 2 (right).

the chloride 106 mEq per liter. The stool electrolyte analysis showed the sodium 135 mEq, the potassium 5.6 mEq and the chloride 143 mEq per liter and chloride concentration was higher than sodium plus potassium concentration. The stool pH was 6.0. A small bowel series showed no obstructive lesion in the small bowel or in the large bowel.

Watery diarrhea persisted and electrolyte abnormality and metabolic alkalosis developed on the third day of life (Table 2). Electrolyte correction with 0.7% NaCl and 0.3% KCl solution was started on the third day of life. After then his diarrhea waxed and waned, ranging soft stool with frequency of 4-5 times daily and watery diarrhea with frequency of 15-20 times daily, The electrolytes and acid-base status were kept within normal limit with previous electrolyte solution.

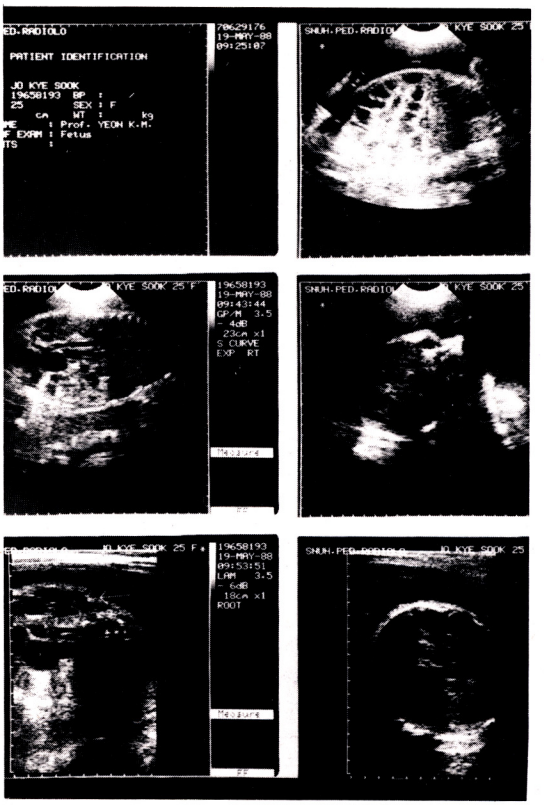

Fig. 3. Prenatal ultrasonography of patient 2. Note polyhydramnios and dilated bowel lumen with fluid.

DISCUSSION

Congenital chloridorrhea is a very rare type of congenital secretory diarrhea which was firstly reported on literature as 'congenital diarrhea with alkalosis' by Gamble (1945) and Darrow (1945).

The patient with congenital chloridorrhea present in the first days of life with the apparantly, paradoxical combination of profuse watery diarrhea and metabolic alkalosis which lead to excessive weight loss and dehydration. Typically the affected infants are premature and products of pregnancies in which there has been some degree of polyhydramnios.

Congenital chloridorrhea causes intrauterine diarrhea resulting polyhydramnios, distended bowel lumen and premature delivery of one to eight weeks. Therefore the prenatal diagnosis of congenital chloridorrhea was possible with ultrasonography (Holmberg 1977, petres 1982, Groli 1986).

On birth the abdomen is usually large and distended due to fluid accumulation in the bowel lumen. In

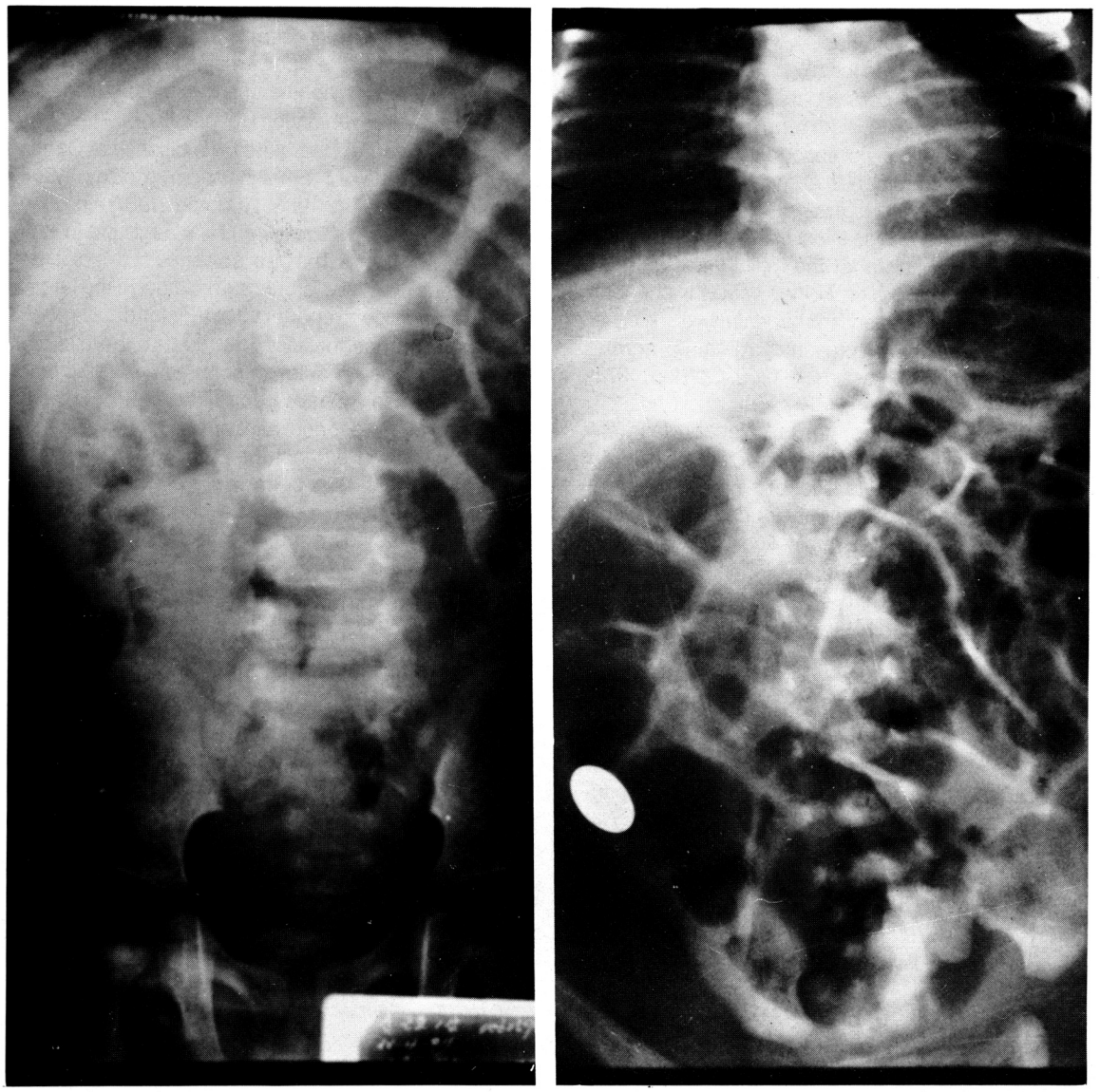

Fig. 4. Simple abdominal X-rays of patient 1 (left) and patient 2 (right). Note marked dilation of bowel loops with fluid and gas.

an impressive number of reported cases the appearance of abdominal distension with a marked 'bladder pattern' has led to laparotomy because of supposed intestinal obstruction. Soon after birth watery diarrhea starts but detection of diarrhea might be delayed several days to several weeks because the diarrhea is so watery that this might be regarded as urine (Holmberg, 1977). On the first day of life approximately 150 ml of fluid is lost with stool. The chloride concentration in stool is 100-150 mEq per liter, usually about 130 mEq per liter. At the same time chloride is virtually absent from the urine (Holmberg, 1977). The stool pH is between 4 and 6. Serum electrolytes and acid-base status at neonatal period remain normal but from about 5 days of life hyponatremia, hypokalemia, hypochloremia and metabolic alkalosis become evident. If remained untreated, hyponatremia become normalized due to hyperaldosteronism but hypokalemia and hypochloremia persist (Holmberg, 1977). The nature of the defect is still unclear, but is probably an abnormality causing a primary chloride leak into the intestinal lumen. Loss of chloride in excess of

sodium leads to a secondary depletion of potassium. Chloride and potassium depletion in it's turn is known to cause deterioration in function of renal tubules and intestinal absorptive cells (Pearson 1973, Turnberg 1971, Holmberg 1975). The chronic hypovolemia leads to a further series of secondary disorders. Juxtaglomerular hyperplasia is associated with increased secretion of renin, high angiotensin activity and hyperaldosteronism. One effect of the constant operation of this mechanism for the maintenance of normovolemia is to produce kidney vascular changes resembling those seen in hypertensive disease, although the blood pressure remains normal (Perheentupa 1965, Pasternak 1966, Gordon 1972, Holmberg 1977).

Earlier patients with congenital chloridorrhea were treated with KCl only at a dose sufficient to maintain normal serum electrolyte level but most of them remained slightly alkalotic and their urine was chloride free (Pasternak, 1967). Examination of renal biopsy specimens showed hypertensive arteriolar changes, juxtaglomerular hyperplasia, nephrocalcinosis and hyalinized glomeruli in the presence of high renin, angiotensin II and aldosteron activity. High potassium intake enabled sodium to be spared but it evidently did so through hormonal adjustment that caused arteriolar pathology (Holmberg, 1977). After 1972, the treatment of congenital chloridorrhea was done with NaCl and added only enough KCl to meet the individual need for potassium (Holmberg et al., 1977 a)

The diagnosis may be suggested by the serum electrolytes. The chloride is low (50 to 80 mEq per liter). This outstanding abnormality is usually accompanied by a low potassium level and a pH greater than 7.43. The diagnosis is confirmed by examination of the stool electrolytes. The stool chloride concentration is extremely high (130-150 mEq per liter) and exceed the sum of the sodium and potassium concentrations.

Mental retardation (Darrow 1945, Owen 1964) and growth retardation (Holmberg, 1977) were evident without therapy but with commencement of adequate electrolyte substitution catch-up growth was possible and cessation of progression of mental retardation was possible. The mortality of the reported cases was high. However, it has been shown that provided satisfactory supplements of oral potassium chloride are given (usually greater than 4 g KCl, daily) and provided that adequate recognition is given to the patient's critical fluid balance (especially during febrile illness or in periods of warm weather) the patient may remain well and thrive normally. With increasing age, diarrhea do not subside. On the contrary, volume tended to increase slightly but chloride requirement seem to be slightly decreased. The character of the stool remains abnormally loose, but after the first months of life, this causes the patient little inconvenience (Holmberg, 1977).

Up to date it appeared to be a disease of Caucasian especially of Finnish origin (Kelsey 1954, Holmberg 1977 & 1985, Rudolph 1987). In orientals, single case was reported by Yanagisawa in 1968 among Japanese. The true incidence of this disorder in various countries is unknown although the largest series has been reported from Finland.

The evidence there suggested that the disorder is inherited as an autosomal recessive trait (Norio, 1971). Both sexes have been affected and two sibs appear to have been affected in several families (Kelsey 1954, Perheentupa 1965).

There might have been some overlooked cases of congenital chloridorrhea among many patients with chronic diarrhea in which etiology was unestablished.

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