A Case of Neonatal Diarrhoea Caused by Congenital Glucose-galactose Malabsorption

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SUMMARY

A five-month old Indian girl, product of consanguineous marriage, presented with diarrhoea with an onset within two days after birth, severe malnutrition and metabolic acidosis. The diarrhoea persisted even with lactose-free formula, amino acid-based formula and glucose-containing oral rehydration solution, but stopped when fasted. She required prolonged parenteral nutrition. Fructose and glucose tolerance tests were performed, confirming the child was able to absorb and metabolize fructose but not glucose, indicating a diagnosis of glucose-galactose malabsorption. This case illustrate how simple and pertinent clinical observations and laboratory investigations is sufficient to allow a firm diagnosis to be made.

KEY WORDS:
Glucose-galactose malabsorption, Neonatal diarrhoea

INTRODUCTION

Diarrhoea with an onset within the first few days of life is rare and is generally caused by congenital malabsorptive disorders[1]. Diagnosis should preferably be made as early as possible to institute appropriate therapeutic measures as these young infants have very little nutritional reserves. We describe a case of diarrhoea with onset within a few days after birth to illustrate how simple and pertinent clinical observations and laboratory investigations is sufficient to allow a firm diagnosis to be made.

CASE REPORT

TS, a 5-month-old Indian girl, was referred to University of Malaya Medical Centre (UMMC) for further evaluation of neonatal onset of diarrhoea which started at day 2 of life.

She was delivered after a full-term, uneventful pregnancy, with a birth weight of 2.9kg. There was no history of polyhydramios or maternal gestational diabetes. She was breastfed since birth and passed meconium at first day of life. She started to pass watery stools with small amount of faecal material from day two of life, up to five times a day. No other signs or symptoms such as vomiting, bloody diarrhoea, abdominal distension, rash, fever or respiratory symptoms were noted. Her feeding remained well. She was discharged at day five of life.

The diarrhoea became more frequent after discharge, up to 10 times a day and the stools were watery. It was foul smelling and overflowed her diaper. However, they were not oily or blood stained. Her breastfeeding remained well.

At day 14 of life, TS became more lethargic and refused to feed. She was admitted to a local hospital, where she was found to have severe hypernatraemic dehydration and metabolic acidosis. The body weight on admission was 2.3kg. Parenteral nutrition (PN) was started. Various types of infant formulae, including lactose-free formula and amino acid-based elemental formula (Neocate®, Scientific Hospital Supply, Liverpool, United Kingdom) were tried but the diarrhoea persisted. The diarrhoea persisted even with oral rehydration solution (ORS) and oral medications. The diarrhoea was markedly reduced when she was kept nil orally. Investigations for underlying immune deficiencies, infective and metabolic screens were all negative. A sweat test was attempted but the sample of sweat was insufficient.

PN and enteral infusion of Neocate® were both continued. With this, her stool output was 1000-1500 ml/day (up to 10-15 times a day). She was referred to UMMC at five months of age.

She is the product of a consanguineous marriage; her father is the uncle of her mother. Her third elder brother passed away at a local hospital at 29 days of life after protracted diarrhoea which started at day 5 of life. No firm diagnosis was made.

At UMMC, the body weight was 4.7kg (<3rd percentile, corresponding to 50th percentile of a 3-month-old girl), length was 60cm (at 3rd percentile) and head circumference was 39cm (<3rd percentile, corresponding to 50th percentile of a 3-month-old girl). She was pale but has no dysmorphism, jaundice or rash. Her hair was sparse. The muscle bulk at the gluteal region and subcutaneous fat at the mid-arm were reduced. No bony deformity, rib rosary, oedema or cataract was noted. The hydration was fair. No organomegaly noted. Cardiovascular, respiratory and neurology systems were normal. There was mild perianal excoriation. Developmentally she was approximately four months of age. The stools were watery.

Investigations revealed mild hypochromic microcystic anaemia (Hb 78 g/L). The white cell count and platelet count were normal. Electrolytes, urea and creatinine, liver enzymes were all within normal limits. There was mild metabolic acidosis. Stool ova and cyst, rotavirus, culture for bacterial pathogen, occult blood and fat globule were all negative. PN was continued but the Neocate® was stopped. Only plain

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Table I: Serial glucose- and fructose-containing fluid challenge tests

	Serial blood sugar	
Time after challenge	Fructose challenge (mmol/L)	Glucose challenge mmol/L)
0 min	3.6	6.5
30 min	5.0	6.7
60 min	7.6	6.4
90 min	5.5	6.1
120 min	5.6	5.6
Stool output throughout challenge	No diarrhoea throughout the test	Large amount of watery stool, 230g at the end of the test, stool reducing sugar positive.

water was allowed orally. Immediately, the stool output markedly reduced to three times per day.

The provisional diagnosis was glucose-galactose malabosrption (GGM). Supporting features include the early onset of diarrhoea, parental consanguinity and a family history of early neonatal death due to diarrhoea in an elder sibling. The persistence of diarrhoea even with ORS but marked improvement when kept nil orally suggests osmotic diarrhoea with intolerance to glucose.

Fructose and glucose tolerance tests were performed (Table I). The patient was fed with 1g/kg body weight of fructose and glucose, respectively on two separate occasions. Serial blood sugar monitoring was performed. The fructose challenge test showed clear absorption of fructose with subsequent conversion into glucose *in vivo*, with no diarrhoea. Malabsorption of glucose was also demonstrated (Table I). The final diagnosis is GGM.

The parents were given appropriate counseling about the autosomal recessive pattern of inheritance of this condition. The child was started with carbohydrate-free formula (Galactomine-19®, SHS International, Liverpool, United Kingdom), a fructose-based nutritionally-complete, infant formula. The PN was gradually discontinued. She tolerated well and started thriving. The stool frequency improved and she passed more formed stools 2-3 times per day. She is at present thriving and symptom free six months after the diagnosis, and is able to tolerate low-carbohydrate weaning food.

DISCUSSION

Differential diagnoses of any patient with early onset neonatal diarrhoea are limited and include: congenital microvillus atrophy, tufting enteropathy, congenital GGM, congenital lactase deficiency, congenital malabsorption of chloride and sodium, bile acid malabsorption, and congenital enterokinase deficiency[1].

Both congenital microvillus atrophy and congenital chloride diarrhoea usually cause secretory-type of diarrhoea and are therefore unlikely to be the cause of diarrhoea in this child. In addition, there was no history of polyhydramios. The initial hypernatraemic dehydration makes the diagnosis of congenital sodium diarrhoea unlikely. Congenital lactase deficiency can be excluded as the diarrhoea persisted even with lactose-free formula. As the stools were not steatorrhoeaic, congenital bile acid malabsorption is unlikely. Congenital enterokinase deficiency is less likely as her diarrhoea persisted even with ORS.

Parental consanguinity, a positive family history of similar presentation of neonatal diarrhoea in an elder sibling, the osmotic nature of diarrhoea with persistence of diarrhoea even with ORS all suggests the diagnosis of GGM. The glucose and fructose tolerance tests confirmed the diagnosis.

GGM is a rare autosomal recessive disease,[2] first reported in Sweden and France in 1962[3]. Currently only about 300 cases have been reported worldwide[2]. The first case of GGM from Malaysia was reported in this medical centre by Lee WS in 1997[4].

Lactose, the primary disaccharide present in breast milk, is hydrolyzed by lactase on the external surface of the intestinal brush border[2]. The liberated glucose and galactose are then transported across the brush border membrane by the Na+/glu co-transporter (SGLT1) and accumulate within the enterocyte. SGLT1 is responsible for the tight coupling of two Na+ ions and one sugar molecule across the membrane[2].

GGM is caused by a defect in the intestinal SGLT1 which is located on chromosomal 22q13.1[2]. Lactose found in breast milk is hydrolyzed normally but absorption of glucose and galactose is absent or reduced, leading to osmotic diarrhoea. Undigested glucose and galactose are then delivered to the colon and fermented by colonic bacteria producing short chain fatty acids. The stools become acidic.

Affected infants usually present with diarrhoea within the first few days of life with severe life threatening diarrhoea with hyperosmolar dehydration and metabolic acidosis during the neonatal period[2]. As the pathogenesis of diarrhoea is osmotic, the diarrhoea resolves once enteral feeding is removed. The stool pH is usually < 5.3 and stool reducing sugar is positive with large stool osmotic gap > 40 mOsm.

A firm diagnosis of GGM can be established by the demonstration of a complete resolution of diarrhoeal symptoms following complete elimination of glucose and galactose (and lactose) from the diet, as well as a demonstration of absorption of fructose but not glucose[2].

These two features have been adequately shown in the present case. Other authors also advocated the demonstration of a normal small bowel intestinal histology[2]. Currently, genetic testing is not necessary for confirmation of diagnosis as there are many mutations (46 types) in the SGLT1 gene and the test is costly and time consuming.

The mainstay of the management is elimination of glucose and galactose from the diet. Currently there are two types of carbohydrate-free formula, namely Ross carbohydrate-free formula (RCF®, Abbott Laboratories, Illinois, USA), and Galactomin 19® (SHS International, Liverpool, United Kingdom). Both of the formulae can be supplemented with fructose to provide carbohydrate in the diet.

The medium term prognosis of GGM is usually good. As the patients grow older, most can tolerate some amount of glucose with no diarrhoea, the unabsorbed glucose being fermented by colonic bacteria. The main concern for this group of patients is the compliance to these special formulae and the long term consequences of taking a high protein and fat diet[2]. The required life-long glucose- and galactose-free diet may have significant renal and cardiovascular consequences.

In summary, we describe a case of congenital GGM, illustrating how simple and pertinent clinical observations and laboratory investigations together with a sound understanding of the physiology of normal absorption, is important to make a firm diagnosis of a rare but potentially fatal condition.

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