Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 9 Issue 2 February 2026

Case Report

An Unusual Case of Delayed Meconium Passage: Guanylate Cyclase C Mutation in a Neonate

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Received: January 23, 2026

Published: February 27, 2026

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Abstract

Background: Guanylate Cyclase C (GC-C; Gucy2c) is a transmembrane receptor that is expressed in the intestinal epithelial cells and activation of GC-C by its secreted ligand guanylin stimulates intestinal fluid secretion. Familial mutations in GC-C cause chronic diarrheal disease or constipation and are associated with intestinal inflammation and infection.

Clinical Description: We describe a case of meconium ileus with an unusual presentation and underlying cause. The newborn presented with non-passage of meconium and cystic fibrosis was suspected but immunoreactive trypsinogen levels were normal. Whole exome sequencing helped establish a diagnosis.

Management: A multidisciplinary follow-up including medical geneticist and pediatric gastroenterologist was arranged. The child has been on regular follow-up, with a normal growth and development and has had no further gastrointestinal issues.

Conclusions: High index of suspicion and detailed diagnostic work up are required for early diagnosis and management of GUCY2C mutations.

Keywords: GUCY-2C Mutation; Familial Diarrhea; Neonate; Cystic Fibrosis; Intestinal Obstruction; Genetic Disorder

Introduction

Timely passage of the first stool is a hallmark of the well-being of the newborn. Delayed or non-passage may represent a number of clinical conditions ranging from Anorectal malformations, Hirschprung's disease, intestinal atresia, neonatal sepsis, asphyxia, Predisposition to meconium ileus in cystic fibrosis is determined genetically [1,2].

Meconium ileus (MI) is a unique phenomenon in infants with CF and represents the earliest clinical abnormality with a prevalence of 10% to 21% [3], the meconium is highly viscid, desiccated, and inspissated, leading to intestinal obstruction [3].

Here we report a case of a newborn with an unusual manifestation of meconium ileus.

The purpose of this report is to create awareness among clinicians so that they consider newborns presenting with meconium ileus should undergo whole exome sequencing with attention towards the GUCY2C gene.

Clinical Description

A male baby born to a non-consanguineously married couple, at full term (38 weeks), had a normal antenatal course with normal blood work and scans. The baby cried immediately after birth and had APGAR scores of 9/10 and 9/10 at 1 and 5 minutes respectively. He had a low birth weight of 2160 grams but normal length and head circumference for the gestational age. Head to toe and systemic examination was essentially normal.

The baby had a normal transition. He remained with the mother and fed properly, maintained adequate urine output and had a normal postnatal sugar levels.

On day 2 of life the baby had 3 episodes of milky vomiting and one episode of bilious vomiting. He had still not passed meconium and was shifted to the NICU. The vital parameters and systemic examination were normal.

He thereafter developed respiratory distress thereafter and nasal high flow nasal cannula was started.

Early onset neonatal sepsis with possible ileus and surgical conditions of the abdomen were considered at that point and the pediatric surgeon was involved.

Management and outcome

Intravenous antibiotics were started. The C- reactive protein was positive (76.12 mg/L). Bilious vomiting continued and meconium wasn't passed. He was kept nil per orally and an upper gastrointestinal dye study showed Grade II gastro esophageal reflux, normal small bowel loops and a normal rectal shadow. He passed a white, discoloured meconium plug after a colonic wash. Contrast enema for diagnosis and treatment was given on day 3, which showed microcolon, subhepatic caecum and pellets of meconium in the distal ileus. Pediatric surgeon advised. Acetylcystein and Erythromycin for dislodgement of meconium. Domperidone and Lansoprazole were also started. Feeds were restarted on day 4 and full feeds were reached on day 7 and a normal stool pattern was noted during this period.

The CRP gradually reduced and became negative and the blood cultures were sterile and the antibiotics were stopped after 7 days. All the baseline blood workup was normal.

Immunoreactive Trypsinogen was checked twice for CF (cystic fibrosis) screening but was not elevated either time.

After discharge, the baby was followed up regularly and remained well, and did not develop any issues with the passage of stools or any respiratory problems.

Whole exome sequencing was carried out to detect mutations related to cystic fibrosis. A heterozygous missense variation in exon 18 of GUCY2C gene (Chr 12:g.14641153T>C; Depth :154X) resulting in amino acid substitution of cysteine for tyrosine at codon 66 (p.Tyr 666Cys: ENST00000261170.5) was detected (MedGenome Labs, Bangalore).

A multidisciplinary follow-up including medical geneticist and paediatric gastroenterologist was arranged. Close monitoring was advised and possible manifestations associated with GUCY2C-associated genetic conditions were explained to the parents.

The child has been on regular follow-up and till his most recent review at 4 years of age, and no gastrointestinal issues have appeared. He remains clinically well, with normal growth and development.

Discussion

The first stool is passed within 24 hours of birth in 99% of healthy full term neonates [4]. Delayed passage may be associated with disorders such as Hirschprung's disease, meconium plug syndrome, small left colon syndrome, congenital hypothyroidism, meconium ileus secondary to neonatal sepsis [4].

Non-CF meconium ileus is caused by an array of etiologies ranging from defects in intestinal innervation to pancreatic insufficiency and meconium plug syndrome to anorectal malformation [4]. Some of the differential diagnosis being Hirschsprung disease, meconium plug syndrome, meconium ileus, anorectal malformations, small left colon syndrome, and intestinal atresias.

Hypothyroidism, sepsis, and electrolyte abnormalities (hypercalcemia, hypokalemia), and maternal medications (magnesium sulfate, illicit drugs) can also delay the passage of meconium.

In 2012, Romi., *et al*. [2] reported two unrelated consanguineous Bedouin kindreds, who presented with meconium ileus, without pulmonary or pancreatic features of cystic fibrosis. Mutations were identified in the GUCY2C gene, which encodes guanylyl cyclase 2C, a regulator of ion and fluid balance that is predominantly localized at the apical brush border membrane of the intestinal epithelium [4].

An autosomal dominant familial diarrhea syndrome has been reported in a Norwegian family due to a change in the GUCY2C gene [5]. This was found to be because of a missense mutation in

the catalytic domain (c.2519G4T: p.Ser840Ile), resulting in a gain of function.

Amanda Smith., *et al*. reported a third case that supports the association of variants in the GUCY2C gene with meconium ileus . A Lebanese kindred was studied and individuals affected with meconium ileus had either homozygous or compound heterozygous variants in GUCY2C [6].

The earliest manifestation of the affected individual can be the presence of second trimester echogenic bowel. GUCY2C expressed in the human intestine and encoded protein activates the CFTR protein via generation of cGMP [7]. GUCY2C encodes GC-C , an intestinal transmembrane receptor with known function in the heat stable enterotoxin mediated diarrhoea [8].

An activating mutation in GUCY2C , can be a cause of novel familial diarrhoea syndrome characterized by dysmotility , abdominal pain , inflammatory bowel disease. GUCY2C can be a susceptible gene for Crohn's disease, small bowel obstruction , gastrointestinal disease [5]. Familial GC-C mutations demonstrate that epithelial cGMP signalling is critical to electrolyte and fluid balance in the neonatal intestine [5]. Chronic deregulation of GC-C activity in early life increases susceptibility to a number of disorders, including obstruction and inflammatory bowel disease [3]. Therapeutic GC-C ligands are used to successfully treat constipation-predominant irritable bowel syndrome and recent studies show that extracellular cGMP is an important mechanism of reducing abdominal pain associated with this disorder [9].

As the previously reported cases has a familial occurrence of diarrhea or recurrent episodes of chronic diarrhea contrastingly our case showed no such signs and symptoms. Ours is the first report with follow-up date well beyond infancy. The child is developmentally normal and has not displayed any major gastrointestinal symptoms.

The expression of the GUCY2C is the highest in the newborn period and does not appear to have any pancreatic or pulmonary complications. The fact that this is a self-limited condition may explain why there have not been other reports of GUCY2C associated meconium ileus.

GC-C-CFTR pathway is to be studied more to understand the underlying mechanism.

Conclusion

GUCY2C mutations can be considered when evaluating a neonate with delayed meconium passage after the common causes have been ruled out. A high index of suspicion and detailed diagnostic work up is required for early diagnosis. A multidisciplinary team approach ensures best results with minimal complications. The expression of this mutation is highest in the newborn period and does not have any pancreatic , pulmonary complications.

Conflicts of Interest

There are no conflicts of interest.

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