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Meconium ileus in Cystic Fibrosis

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Abstract

Meconium ileus (MI) is often the first manifestation of cystic fibrosis (CF) and occurs in approximately 20% of patients diagnosed with CF. This article reviews the pathophysiology of MI and its clinical presentation. It focuses on the medical and surgical management emphasizing the importance of nutrition and a multidisciplinary approach to improve both short-term and long-term outcomes for CF patients with MI.

Keywords: Meconium ileus; Meconium peritonitis; Gastrografin; Cystic fibrosis

1. Background

Meconium ileus (MI) is often the first manifestation of cystic fibrosis (CF) and occurs in approximately 20% of patients diagnosed with CF. It can present in two forms, simple MI and complex MI. In simple MI, viscid meconium physically obstructs the terminal ileum and the small intestine proximal to the obstruction, then becomes dilated with additional meconium, gas, and fluid [1]. In complex MI, the meconium-distended segments of ileum can give way to complications like prenatal volvulus, ischemic necrosis, intestinal atresia, or perforation and extrusion of the meconium into the peritoneum. The timing of perforation may contribute to the outcome. If perforation occurs earlier in utero, there is the possibility of reabsorption of some meconium in the peritoneum before delivery, leaving only a small number of calcifications. If necrosis and perforation occur close to delivery, meconium peritonitis is more likely to be seen. Meconium may also become (partly) encapsulated: giant cystic meconium peritonitis (GCMP) [2–3]. This condition may present with a palpable mass on exam in a patient with MI or meconium peritonitis [1]. Both simple and complex MI occur with similar frequency in patients with CF.

Understanding the pathophysiology of MI has been greatly advanced by the development of mouse models as well as the cystic fibrosis transmembrane conductance regulator (CFTR) knock out ferret and pig, which have 100% penetration of MI. Within the small intestine, CFTR is responsible for both Cl^- and $HCO3^-$ excretion. It is the $HCO3^-$ that plays an integral role in chelating Ca^{2+} associated with the tight matrix of normally exocytosed mucins within the gut lumen to form normal, loose well-hydrated mucus [4]. Abnormal CFTR results in abnormal $HCO3^-$ secretion, thus decreasing luminal pH. This creates an acidic and dehydrated environment in which the tight matrix of exocytosed mucins are not disrupted appropriately resulting in thick, dehydrated mucus [4]. The abnormally acidic luminal environment also promotes the presence of elevated levels of stool albumin, increased mineral content, and protein-bound carbohydrates. These combine with the dense mucus to form viscid meconium that eventually leads to physical obstruction of the terminal ileum (TI) [1,4–6]. This process might result in the two outcomes described above, either simple or complex MI.

MI is most commonly associated with class I-III CFTR mutations. Specifically, MI is associated with F508del, G542X, W1282X, R553X, and G551D [7]. Based on the United States CF

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Patient Registry 2010 database, a patient with two copies of the most common F508del mutation has a 24.9% risk of presenting with MI [7]. A patient with a F508del paired with another mutation has a 16.9% risk of presenting with MI [7]. The risk of a patient with two other CFTR mutations presenting with MI is 12.5% [7]. Evaluation for risk of MI in CF monozygotic and dizygotic twins also found an increased concordance in monozygotic twins [8]. In addition, it has been noted that in families where there is a history of an infant with MI, the chance that a subsequent child with CF will develop MI is greater than expected [9–10]. These findings point to the involvement of modifier genes in the development of MI. However, although multiple modifier genes that enhance or reduce the risk of MI have been identified in single studies, the ability to replicate these results has been limited [8–13].

With better understanding of CF and earlier recognition of MI, there have been significant improvements in the morbidity and mortality associated with MI. Mortality rates, as high as 33% in the 1960s for both simple and complex MI, have significantly improved [14]. Today, early and late survival rates for both simple and complex MI are consistently reported over 80% [1–2].

The first significant improvement came in 1948 when Hiatt and Wilson described a method for intraoperative disimpaction of MI with saline [15]. This was followed in 1969 with Noblett's description of using hyperosmolar Gastrografin enemas in the management of simple MI [16]. At the time, this novel technique aided in the minimization of small bowel and colonic resection in simple MI. In addition, the development of a comprehensive multidisciplinary approach to the care of CF infants by pediatric surgeons, neonatologists, pulmonologists, respiratory therapists, gastroenterologists, and dieticians has not only led to further improvements in short-term morbidity, but has also allowed for negligible long-term differences in regards to nutritional status, pulmonary function, and infection status for CF patients with history of both simple and complex MI [17–19].

2. Clinical presentation and differential diagnosis

In the modern era of highly sensitive medical technology, MI and meconium peritonitis are often detected prenatally by the presence of hyperechoic bowel or peritoneal calcifications on ultrasound (US) [20]. However, hyperechoic bowel can also be seen in many other disease processes [20]. A 16 year review of US experience in Brittany, France from 1992 to 2007 found that only 7.6% of 289 patients who had abnormal bowel detected by prenatal US actually had CF. Nevertheless, if hyperechoic bowel is detected, it is imperative to assess the fetus's risk of CF [20].

If not identified prenatally, the most common clinical presentation of MI is intestinal obstruction, which is often seen within hours of birth. When feedings are initiated, bilious emesis occurs with or without abdominal distention. The infant with meconium peritonitis often presents with additional signs of abdominal tenderness, fever, and shock [1]. Other infants may only display concern for MI with the delayed passage of meconium. In all of these cases, the differential diagnosis includes not only CF with MI, but also other conditions including meconium plug (hard stool covered with mucous that is difficult to pass), Hirschsprung's disease, jejunoileal atresia, volvulus, and bowel perforation.

3. Diagnostic workup

In the case of an abnormal prenatal US, screening for CF should be offered by assessing the carrier state of the parents, either through a common mutation panel or through sequencing of the whole CFTR gene, understanding the limitations of both. If both parents are noted to be carriers of CF, then appropriate genetic counseling should be offered to discuss the risks of having an infant with CF and future implications. If one or both parents are noted not to be carriers, genetic counseling should still be offered to discuss the limitations of testing as well as other disease processes associated with hyperechoic bowel. (Fig. 1) Once a hyperechoic bowel has been seen on US, the fetus should be followed with US every 6 weeks or less [4]. In addition, referral to a perinatologist should be made so that delivery can be planned at a tertiary care center with an experienced neonatal intensive care unit (NICU) and a multidisciplinary team, including a pediatric surgeon.

Initial workup of any infant with bilious emesis, with or without abdominal distention, requires initial stabilization of the patient including prescribing nothing per os (NPO), establishing intravenous (IV) access, and assuring adequate hydration to maintain good perfusion. Laboratory evaluation, including electrolytes, white blood cell count (WBC), hemoglobin, and lactate, is also useful in determining the clinical status of the infant. If fever is present or WBC is elevated it may be appropriate to obtain blood and urine cultures and consider initiation of antibiotic therapy. Often a nasogastric tube (NGT) is placed to allow for decompression of the stomach and proximal small bowel, as well as to prevent further bilious emesis and decrease risk of aspiration. If the infant is not already in a NICU under the care of a multidisciplinary team including pediatric surgeons, neonatologists, and gastroenterologists, transfer should be arranged immediately.

In an infant that presents with bilious emesis, the assumption is that there is a small bowel obstruction (SBO). Evaluation for its etiology begins with basic abdominal films. Usually both flat and upright films are needed. In MI, abdominal films often show dilated loops of bowel with or without air-fluid levels. Air may not be present in the rectum if there is a complete obstruction. Abdominal calcifications may be present if there has been a contained or now closed intestinal perforation. The classic "soap-bubble" sign seen when meconium mixes with swallowed air may also be appreciated in the distal small intestine (Fig. 2) [21]. If abdomen is distended and peritoneal signs are present on physical exam or if the infant is hemodynamically unstable, assumption of complex MI will be made and the infant will be taken emergently to the operating room (OR). In a stable infant, a diagnostic contrast enema may be beneficial in detecting a microcolon due to proximal obstruction in the TI and disuse below the obstruction, as well as malrotation by localizing the position of the cecum. If malrotation is suspected based on results of the contrast enema, an upper gastrointestinal series (UGI) needs to be done to confirm diagnosis of malrotation and to better