MECONIUM ILEUS EQUIVALENT: AN ADULT COMPLICATION OF FIBROCYSTIC DISEASE

DONALD B. HUNTON, M.D., WALTER K. LONG, M.D., AND HENRY Y. TSUMAGARI, M.D.

The Frances Warren Pershing Memorial Hospital and the Richardson Memorial Laboratory, Cheyenne, Wyoming

Meconium ileus is predominantly a disease of infants who have fibrocystic disease of the pancreas, occurring in about 10% of those with the affliction.1 There are reports in the literature of fibrocystic patients developing intestinal obstruction from impacted fecal material at ages beyond the neonatal period. However, such an occurrence has rarely been reported beyond the age of 15 years, and this disease is not widely described in the gastroenterological literature. The only current comments on fibrocystic disease are from Di Sant'Agnese and Lepore2 and from Lepore3 who discuss various intestinal aspects but not intestinal obstruction. There are available excellent and comprehensive descriptions of fibrocystic disease in adults,3-8 but these are concerned with the genetic, pancreatic, and pulmonary components of the disease. Only recently have authors begun to describe the intestinal lesions. Mendeloff7,8 as recently as 1962, felt it wisest to state that only "perhaps" the gut is involved. Then in 1963, Thomaidis and Arey9 described the intestinal gland changes but concluded that these findings were not as important as pancreatic disease in the production of symptoms.

McIntosh,10 in 1954, reported 23 patients older than age 10 years who had intermittent abdominal pain of undetermined cause. In 1956, Di Sant'Agnese11 reported that the intestinal glands were occasionally involved in the abnormal mucoid formation, but stated that at that time there were no recognized symptoms. In 1959, Di Sant'Agnese and Anderson1 observed that right lower quadrant masses which usually passed spontaneously could be found in these children. In 1961 Di Sant'Agnese and Lepore2 postulated that these masses were composed of abnormal feces, perhaps being an expression of abnormal intestinal mucus.

Rizk and Kissane12 stated in 1959 that the gut was macroscopically normal. However, in 1961, Brown and Wilson13 described the gut as containing a waxy, yellow, pliable material which adhered firmly to the gut wall so that bleeding occurred when it was stripped away.

Microscopic examination of the intestinal villi has been reported variously. Marks and Anderson14 found a normal villous pattern on small bowel biopsy; but Jensen15 found the villi absent in his patient. Bodian,16 in 1952, in his excellent monograph observed that the villous mucous cells in infants were not conspicuous in numbers. Brunner's glands contained a marked amount of an eosinophilic homogenous or basophilic vacuolated secretion. This same secretion was seen distending the crypts of Lieberkühn into which Brunner's glands emptied. The involvement of Brunner's glands was confirmed by Rizk and Kissane.12 These authors also reported mucous cell dilation of the duodenal villi, an observation later confirmed by Marks and Anderson,14 Porcoro and Soranno,17 and Jensen.15

Fibrocystic disease of the pancreas is a
generalized, inherited disease of exocrine glands characterized by histologically abnormal mucous glands which secrete a highly viscid mucus, and sweat glands and salivary glands which, though normal morphologically, secrete abnormal amounts of sodium chloride. As pointed out by Di Sant’Agnese,\(^1\) this means that the names “fibrocystic disease” and “mucoviscidosis” are both inadequate. We shall therefore employ the former name by reason of its historical seniority and wider familiarity.

The earliest report associating meconium ileus with disease of the pancreas was made by Landsteiner\(^1\) in 1905 in an autopsy report on an infant. In 1933, Blackfan and Wolbach\(^2\) first noted that the pathological process in the pancreas appeared to consist of inspissation of secretions. Cystic fibrosis of the pancreas was described as a disease entity, and given its name by Fanconi et al. in 1936.\(^3\) It was not widely recognized until 1938, however, when it was simultaneously reported in the United States by Anderson,\(^4\) Blackfan and May,\(^5\) and Harper.\(^6\) These authors all described the malnutrition, steatorrhea, and pulmonary aspects of the disease, attributing the gastrointestinal features to pancreatic insufficiency.

The direct relationship existing between fibrocystic disease and neonatal meconium ileus has been subsequently well documented by Hiatt and Wilson,\(^7\) Lyall and Michie,\(^8\) and Schwachman et al.\(^9\) There are reports of intestinal obstruction due to inspissated fecal material occurring “late” (beyond the neonatal period) in this disease. The authors have found 26 such cases reported by Rasor and Stevenson,\(^10\) Levy,\(^11\) Fisher,\(^12\) Schwachman and Leubner,\(^13\) Birse,\(^14\) Schwachman et al.,\(^15\) Brown et al.\(^16\) (these authors reported three cases but we have omitted the patient with a polyp), Porcoro and Soranno,\(^17\) Fanconi,\(^18\) Brown and Wilson,\(^19\) Cordonnier and Izant,\(^20\) Snyder et al.,\(^21\) Mullins et al.\(^22\) and, finally, Jensen\(^23\) who, in 1962, coined the excellent name of “meconium ileus equivalent.” The ages of the reported patients were 2, 4, 7, 10, 13, 14, 15, 16, 18, and 22 months; and 2, 2, 4, 4, 5, 6, 7, 9, 11, 11, 13, 15, 15, 20, 25, and 31 years.

The clinical features suggesting the diagnosis of meconium ileus equivalent are reported to include: (a) intestinal obstruction in any patient suspected of being fibrocystic;\(^24\) (b) pain and tenderness over McBurney’s point;\(^25\) (c) a soft indentable mass in the right abdomen;\(^26,27\) and (d) plain abdominal X-ray showing bubbly appearing material (Neuhauser’s sign).\(^28\) The case herein described is one of the oldest cases of meconium ileus equivalent. It serves to demonstrate the diagnostic and therapeutic difficulties encountered as well as the pathological findings in the intestine.

**Case Report**

The patient was a 20-year-old single white man who had a history dating to the age of 1 month when he was noted by his parents to have foul, bulky stools and a protuberant abdomen. At the age of 21 months, the diagnosis of fibrocystic disease of the pancreas was made at a regional medical institution. Even on a sprue diet he developed poorly, having many respiratory infections. An X-ray of the chest at age 5 years showed prominent lung markings without definite ectasia. He had a brief sojourn in the United States Navy in 1960 where a lung biopsy reportedly showed pulmonary fibrosis. Treatment with corticosteroids was begun at that time. In November 1961, a second regional medical center found that his pulmonary disease was extensive. At that time a sweat chloride of 139 meq per liter provided further confirmation of the diagnosis of fibrocystic disease of the pancreas.

When he was first seen by one of us (D. B. H.) at age 19 in May 1962, he was taking prednisone, 10 mg daily, and oxytetracycline which he used sporadically. He complained of fatigue, dyspnea, cough, recurrent bronchitis, and some tendency to foul bulky stools. Examination at that time revealed the signs of chronic pulmonary disease with poor nutrition, poor development, barrel chest, severe clubbing, cyanosis, and wet rales throughout the lungs.

He was gradually withdrawn from prednisone and placed on adequate doses of antibiotics and expectorants. On this regimen, he remained reasonably stable and gainfully employed for the next 18 months. An initial attempt was made to use pancreatic replacement therapy. He refused this after a brief trial because he observed no subjective improvement and felt the cost was excessive for him.

On 5 September 1963, he was hospitalized
briefly at the DePaul Hospital with abdominal pain. A tentative diagnosis of duodenal ulcer was based on X-ray evidence of duodenitis and a dramatic response to ulcer therapy, although his initial pain was not typical. He left the hospital after 3 days and was not seen again until 10 January 1964. At this time, the final admission to Frances Warren Pershing Memorial Hospital was made because of dyspnea. His initial pain was not typical. He stated on admission that he had had crampy periumbilical pain every night for several weeks but had not sought treatment.

A chest X-ray revealed chronic pulmonary disease with pulmonary hypertension. An electrocardiogram showed low posterior T waves. The initial hemoglobin was 14.8 g per 100 ml, hematocrit was 48%, and white blood cells 11,900 per mm³. Urinalysis revealed a 1+ albumin. The findings pertinent to the purpose of this paper were limited to the gastrointestinal tract. The pancreas with its attached fat weighed 40 g. The consistency was firm and the anatomic relationships were unchanged. The external configuration did not appear abnormal. The cross-section showed a decrease in the lobules and the ducts appeared distended with a viscous clear material.

For the following 6 days an attempt was made to relieve the completely obstructing ileus with nasogastric suction and introduction of pancreatic enzymes. On the 6th postoperative day his condition deteriorated rapidly with a sodium of 120 meq per liter, potassium of 4.9 meq per liter, chloride of 62 meq per liter, and carbon dioxide of 35 mmoles per liter.

At this time it was decided that re-exploration with surgical removal of the fecal material was mandatory. He was taken to surgery where a moderate wound dehiscence and hematoma were found. The lower one-third of the small bowel was dilated to 6 cm with ininspissated material, some of which was also present in the left colon. About 18 inches proximal to the ileocecal valve, a transverse enterotomy was made and the fecal material massaged out. Number 20 Fr catheters were then inserted proximally and distally for irrigation. A gastrostomy was made for irrigation from above. Finally, a transverse colostomy was brought out in case of future need but was not opened. In the recovery room, the patient developed severe shock which failed to respond to normal saline, pressor amines, and blood transfusion. He died at 7 AM on the first postoperative day.

Necropsy Findings

The significant histopathological changes demonstrated were in the duodenum, jejunum, and ileum. The duodenal acinar glands and Brunner's glands as shown in figure 1 are seen to be distended by a mucous material. In the jejunum, figure 2, the lumen is distended by ininspissated pasty material which gives the appearance of streaming upward from the acinar glands. In figure 3, the glands of the jejunum are seen to be distended by a laminated eosinophilic ininspissated secretion that appears to be present in the goblet cells as well.

In the ileum, figure 4, the distention of the lumen and acinar crypts by the pasty, meconiumlike material is still greater.
Comments

With the help of antibiotics and improved general medical care, an increasing number of children with fibrocystic disease are reaching adult age. Mendeloff\textsuperscript{7} estimates the number currently at 250 each year. For those reaching maturity, the major problems tend to be pulmonary in nature while, as noted by Di Sant\textsuperscript{\textdegree} Agnese and Anderson,\textsuperscript{1} the gastrointestinal complaints become milder. Certainly the patient reported here suffered from extensive pulmonary disease. However, it appears worthwhile to record that death in adult fibrocystic patients can result from a gastrointestinal phenomenon, meconium ileus equivalent.

Cordonnier and Izant\textsuperscript{35} describe three criteria useful in establishing the diagnosis
of meconium ileus equivalent. The first of their criteria is the development of intestinal obstruction in a known or suspected fibrocystic patient. This criterion applied most pertinently in this instance. We are of the opinion that this single point deserves wider dissemination in the adult gastrointestinal literature. Their second criterion is an indentable mass in the abdomen, an observation made earlier by Di Sant’Agnese and Lepore. Numerous authors report indentable masses in the right lower quadrants in infants with meconium ileus. This criterion was not helpful in the pres-

Fig. 3 (top). Section of jejunum showing lamination of inspissated secretions (H & E, × 430).

Fig. 4 (bottom). Section of ileum showing marked formation of abnormal mucus (H & E, × 100).
ent instance. No mass was detected 4 months earlier or during the final admission. We suspect this may have been the result either of the rigid, acute abdomen or of the enormous amount of material present, giving the entire abdomen a homogeneous consistency. Some caution appears justifiable in the use of this criterion. Finally, the same authors suggest that Neuhauser’s sign of bubbly intestinal contents on the plain abdominal X-rays is a useful diagnostic measure. When our films were reviewed in light of this information, no important differences could be seen from “normal” patients having extensive amounts of feces in the colon. We have reached the conclusion that the most useful criterion is a high index of suspicion for this disease entity.

The traditional view has in the past been that meconium ileus in infants was caused by a lack of pancreatic enzyme which resulted in inadequate digestion of the intestinal contents. This same reasoning has been extended to the “late” occurring meconium ileus equivalent. However, as early as 1946, Glanzmann 38 offered the suggestion that meconium ileus might be due to abnormal mucous secretions rather than to pancreatic insufficiency. In 1951, Levy 29 postulated an interesting explanation along these lines. He suggested that steatorrhea caused by pancreatic insufficiency produces a constant fluxing of the small bowel which might actually protect the patient from meconium ileus rather than cause it. Then in 1952, Bodian 16 again expressed the opinion that enzyme lack might be contributory, but that an abnormal intestinal mucus was the primary cause of meconium ileus. As recently as 1963, Thomaidis and Arey 9 took a somewhat differing viewpoint, observing that in their patients there was no correlation between gastrointestinal symptoms and the degree of gastrointestinal pathological involvement. It should be pointed out, however, that none of their patients had intestinal obstruction. Di Sant’ Agnese and his colleagues 1, 14, 15, 39 have shown that this mucous material is abnormal, having an altered water solubility and being unaffected by trypsin. There appears to be increasingly good evidence that this material originates in the intestinal goblet cells. 9, 11, 14, 15, 39

The present patient showed extensive intestinal involvement which appears to demonstrate a capacity of the intestine to produce large quantities of the abnormal meconium-like substance. This finding provides evidence that the intestinal wall does play a direct role in the pathophysiology of meconium ileus in adults. However, the lack of pancreatic enzyme appears also to be a significant component part since some patients have responded well to enzyme therapy. This point deserves further study as patients become available to test the efficacy of enzyme replacement therapy in warding off mucus accumulation.

Several authors have adopted the position that meconium ileus and the late equivalent can be managed medically, 17, 30, 32, 35, 40 employing nasogastric lavage and enemas of pancreatic enzymes or N-acetyl cysteine. 36 Brown et al. 33 got excellent results with no effort at all to relieve the obstruction. However, at least in the situation where complete obstruction has persisted for 48 hr, the authors are inclined to favor surgical intervention as described by Porraro and Soranno, 17 Hiatt and Wilson, 25 Fisher, 30 Holscaw et al., 41 and Bishop and Koop. 42

The differential diagnosis in this patient included a possible duodenal ulcer. This was not the major source of difficulty even though an ulcer was seen at necropsy. However, the possibility of duodenal ulcer should be kept in mind because there appears to be an increased incidence of ulcer in fibrocystic patients as reported by Di Sant’ Agnese and Anderson, 1 Lepore, 5 and Aterman. 43

Summary

A 20-year-old patient with fibrocystic disease died as a result of meconium ileus equivalent.

An awareness of this possibility in the older age group is probably an important premise to early diagnosis and treatment of this cause of intestinal obstruction.

While enzyme therapy and N-acetyl
cysteine have been used successfully in patients with meconium ileus equivalent, the authors are inclined to feel that early strenuous surgical correction, followed by enzyme irrigation is a preferable procedure in the face of complete obstruction.

The clinical and pathological data presented here provide additional evidence that the intestinal mucosa is affected in fibrocystic disease, and is a primary factor in the cause of meconium ileus equivalent.

REFERENCES

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