Distal intestinal obstruction syndrome and colonic pathologies in cystic fibrosis

The management of abdominal pain in cystic fibrosis can be complicated. Distal intestinal obstruction syndrome is a common cause of pain and obstruction in these patients. Knowledge of the diagnosis and management and of similar presenting symptoms is essential for the hospital doctor.

Cystic fibrosis is the most prevalent autosomal recessive disorder in the western world. The World Health Organization reports an incidence of 1 in every 3000 live births in the European Union and 1 in every 3500 in the USA. Distal intestinal obstruction syndrome is a well-recognized gastrointestinal complication occurring in 10–24% of patients with cystic fibrosis, with reports of the prevalence varying (Dray et al, 2004; Houwen et al, 2010). As such it is an important condition for the on-call surgeon to be able to recognize and to understand the options for management, including medical and surgical options. Other abdominal conditions can present in similar ways to distal intestinal obstruction syndrome. This article presents the evidence surrounding the investigation and treatment of distal intestinal obstruction syndrome and describes other colonic pathologies which may present in a similar way.

Definition and classification

The phenomenon of post-infancy intestinal obstruction in people with cystic fibrosis, originally termed meconium ileus equivalent, was first described in 1945 (Jaffe et al, 1966). An increase in the understanding of the aetiology and pathogenesis of the condition has led to the term distal intestinal obstruction syndrome being favoured.

In 2010, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition carried out a review at their annual conference with the intention of reaching a consensus on a definition of distal intestinal obstruction syndrome and its subsequent management (Houwen et al, 2010). A split definition was agreed, comprising incomplete and complete distal intestinal obstruction syndrome to encompass a range of acute and chronic presentations. Complete distal intestinal obstruction syndrome was defined as radiological and clinical evidence of complete obstruction associated with abdominal distension and a palpable ileocaecal mass in the right iliac fossa. Incomplete distal intestinal obstruction syndrome was defined as colicky abdominal pain or distension coupled with a palpable ileocaecal mass in the right iliac fossa but without evidence of complete intestinal obstruction.

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Aetiology

Distal intestinal obstruction syndrome is characterized by a blockage of the small intestine, normally at the terminal ileum, by a plug of muco-faeculant material (Robertson et al, 2006). Cystic fibrosis is caused by a defect in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein as surmised by McAuley and Elborn (2000). The most common mutation, occurring in 66% of all patients with cystic fibrosis, is the ΔF508 mutation (Zielenski, 2000). Defects in the gene lead to dysfunction of the CFTR protein. CFTR has many functions, including regulation of cross-membrane sodium, potassium and chloride ion transport and water co-transport, as well as interacting with other proteins such as the epithelial sodium channel (McAuley and Elborn, 2000). It is the dysfunction of these actions which, in the intestinal lumen, leads to a decrease in secretions and an increase in absorption of water and sodium. This leads to an increase in the viscosity in the stool, a main factor in the development of distal intestinal obstruction syndrome.

In addition to this various risk factors have been implicated in the development of distal intestinal obstruction syndrome. Colombo et al (2011) listed the risk factors involved in the development of distal intestinal obstruction syndrome (*Table 1*) which are discussed in more depth below.

Meconium ileus

Meconium ileus occurs in infancy in 13–17% of all patients with cystic fibrosis (McAuley and Elborn, 2000). Studies have shown a strong link between distal intestinal obstruction syndrome in patients with cystic fibrosis and

Table 1. Risk factors implicated in the development of distal intestinal obstruction syndrome

History of meconium ileus
Severe genotype
Pancreatic insufficiency
Previous surgery
Post-organ transplantation

from Colombo et al (2011)

a history of meconium ileus in infancy (Morton et al, 2009; Colombo et al, 2011). In Alder Hey in Liverpool, a large tertiary paediatric hospital, a review of 20 years of gastrointestinal surgical practice for cystic fibrosis undertaken by Farrelly et al (2014) reported 35 patients presenting with 80 episodes of distal intestinal obstruction syndrome. In 20 (57%) of these patients a history of meconium ileus was recorded. Although they did not demonstrate a significant causative effect of meconium ileus in distal intestinal obstruction syndrome, they did show that these patients were prone to developing a more severe form of distal intestinal obstruction syndrome often necessitating surgery.

Escobar et al (2005), in agreement with the Alder Hey review, demonstrated that patients with a history of meconium ileus were more likely to develop a distal intestinal obstruction syndrome resistant to medical treatment and requiring surgical intervention. Other series such as Morton et al (2009) showed an 80–100% history of meconium ileus in patients with distal intestinal obstruction syndrome. However, many of these cases were associated with other risk factors such as previous laparotomy and lung transplantation.

While the current evidence has not shown that a history of meconium ileus is directly causative of distal intestinal obstruction syndrome in later life it has shown an increased rate of development of distal intestinal obstruction syndrome in those with meconium ileus and also the development of a more severe form which may progress to require surgical intervention.

Severe genotype

As mentioned earlier several mutations are implicated in the development of cystic fibrosis of which ΔF508 is the most common. However, other mutations do exist with a range of phenotypical severities (Zielenski, 2000). Several studies have looked at the association between the development of distal intestinal obstruction syndrome and the genotype of the CFTR mutation (Zielenski, 2000; Houwen et al, 2010; Farrelly et al, 2014). Dray et al (2004) reviewed 171 patients with cystic fibrosis of whom 27 patients had 43 episodes of distal intestinal obstruction syndrome. They demonstrated that of these 27 patients 25 (92.6%) had a genotype classed as being severe and that in all patients with a severe genotype (n=114), 25 (21.9%) developed distal intestinal obstruction syndrome. In concordance with this Houwen et al (2010) established that 82% of patients with distal intestinal obstruction syndrome across eight cystic fibrosis centres had a severe CFTR mutation, and 54% were the homozygous ΔF508 mutation. It is widely accepted that a severe genotype is associated with a higher likelihood of developing distal intestinal obstruction syndrome.

Pancreatic insufficiency

Cystic fibrosis is the most common cause of pancreatic insufficiency in young people. Ion channel dysfunction leads to abnormally thickened pancreatic juice leading to duct obstruction and consequently acinar cell atrophy, fibrosis and cyst formation. This process leads to a decrease in the exocrine function of the pancreas with a consequent decrease in lipase production, in turn resulting in a high fat content in the stool which is implicated in the increased risk of distal intestinal obstruction syndrome (Robertson et al, 2006). A number of retrospective studies, including Dray et al (2004) and Subhi et al (2014), show a high rate (>80% in the aforementioned studies) of pancreatic insufficiency in patients developing distal intestinal obstruction syndrome. However, although the link between pancreatic insufficiency and distal intestinal obstruction syndrome via decreased lipase production is logical distal intestinal obstruction syndrome can occur in patients without pancreatic insufficiency. This highlights the role of pancreatic insufficiency as a risk factor but not as a direct cause.

Previous abdominal surgery

Cystic fibrosis is a common reason for patients to undergo major abdominal surgery as infants and children. This is the result of a variety of complications including meconium ileus, intussusception, volvulus, pseudocyst formation or gastro-oesophageal reflux disease refractory to medical therapy (Farrelly et al, 2014). Previous abdominal surgery is a major risk factor in the development of future episodes of distal intestinal obstruction syndrome. Escobar et al (2005) reviewed 27 patients with 30 episodes of distal intestinal obstruction syndrome, the majority of whom had undergone previous abdominal surgery. Farrelly et al (2014) demonstrated that patients with a history of previous abdominal surgery, the majority of which were laparotomies for meconium ileus, were more prone to develop distal intestinal obstruction syndrome and subsequently more likely to have a more severe form of distal intestinal obstruction syndrome possibly requiring further surgical intervention. Moreover all of those who had had a previous laparotomy and went on to have further surgical relief of their obstruction had distal intestinal obstruction syndrome complicated by adhesions. A large review of treatment for distal intestinal obstruction syndrome in New Zealand by Subhi et al

(2014) agreed with these factors, quoting an odds ratio of 28.5 for progression to surgery in those with a history of previous laparotomies.

Post-organ transplantation

Lung transplantation has been available for patients with cystic fibrosis since the 1980s when this was first performed in Toronto (Yacoub et al, 1990). There is good evidence that the rate of distal intestinal obstruction syndrome is higher in those in the early postoperative period following lung transplantation. A review conducted at Toronto General Hospital, the first centre to perform bilateral lung transplantation, by Gilljam et al (2003) demonstrated that the rate of distal intestinal obstruction syndrome in post-transplant patients was 20%, comparable to the general population of people with cystic fibrosis. However, they also demonstrated that 50% of these patients had an episode early in the postoperative period. Morton et al (2009) reported a 10.6% rate of distal intestinal obstruction syndrome in their post-transplant population but again demonstrated that 46% of these occurred in the immediate postoperative period at a median of 7 days. All studies showed that, of those developing distal intestinal obstruction syndrome in the early post-transplant period, those who had a history of major abdominal surgery or meconium ileus in infancy were more prone to having a more severe episode of distal intestinal obstruction syndrome and/or requiring surgical intervention (Gilljam et al, 2003; Morton et al, 2009; Subhi et al, 2014).

Clinical features

The presentation of distal intestinal obstruction syndrome results from recurrent episodes of partial or complete intestinal obstruction. Patients experience crampy colicky abdominal pain. This is often generalized although it can localize to the right lower abdomen. There may be abdominal distension and bloating as well as episodes of vomiting (Houwen et al, 2010). An ileocaecal mass may be palpable in the right iliac fossa. The onset of distal intestinal obstruction syndrome is typically acute. The acute onset of right iliac fossa pain with vomiting and abdominal pain can often lead to various other similar diagnoses that will be discussed later in this article. It is important to make a distinction between pathologies and make an early diagnosis. Radiology may have a role to play in making this important distinction.

Imaging

A range of imaging modalities has been reported to be useful in the diagnosis of distal intestinal obstruction syndrome. The simplest and arguably the most useful in the primary assessment of the patient with distal intestinal obstruction syndrome is an abdominal X-ray. The typical picture on a plain abdominal film in distal intestinal obstruction syndrome is that of generalized small intestinal dilatation with a 'bubbly' mass in the right iliac fossa. Plain radiography has a sensitivity of 63% in detecting distal intestinal obstruction syndrome in the first instance (Subhi et al, 2014).

Computed tomography is the current gold standard radiological investigation in identifying intestinal obstruction and recognizing an obstructive mass in distal intestinal obstruction syndrome, and has the added advantage of allowing the physician to precisely identify the point of obstruction (Robertson et al, 2006). Findings on computed tomography include intestinal mural thickening, fat stranding around the terminal ileum and evidence of an obstructing plug. The appendix is routinely distended as a result of mucoid impaction and a diagnosis of appendicitis should not be made unless there is other convincing radiological evidence to that end. Gastrografin enemas may be useful in determining the point of obstruction, although this has been largely superseded by the use of computed tomography (Agrons et al, 1996).

Ultrasonography is another useful investigation and has high sensitivity (85%) in the diagnosis of obstruction. Its use has been also largely superseded by the availability of computed tomography, although it can be useful as an adjunct when patients are too unstable to go to computed tomography or need to avoid radiation exposure. Magnetic resonance imaging may be more sensitive in the diagnosis of the point of obstruction (Jackson and Raiji, 2011) but, again, owing to the relative availability and low cost of computed tomography it is rarely used in diagnosis. It may become further used in the future when multiple serial investigations are indicated in patients having recurring episodes of obstruction (Colombo et al, 2011).

Treatment

Various studies have looked at alternative management strategies in the treatment of distal intestinal obstruction syndrome. No definitive treatment has been established as the inability to blind between surgical and conservative managements makes it impossible to conduct randomized trials in this area.

As mentioned earlier, distal intestinal obstruction syndrome may present within a spectrum of severities encompassing the two definitions of complete and incomplete distal intestinal obstruction syndrome. Treatment should be tailored to the severity of the presentation.

Conservative treatment

A number of studies have advocated the use of the conservative approach first line for those with less severe symptoms (Dray et al, 2004; Morton et al, 2009; Subhi et al, 2014). Varying rates have been reported for the success of conservative management in distal intestinal obstruction syndrome. Davidson et al (1987) was one of the first studies to advocate the use of conservative management. They reported six patients with incomplete distal intestinal obstruction syndrome and one with complete obstruction, treated with oral lavage solution and all achieved relief of

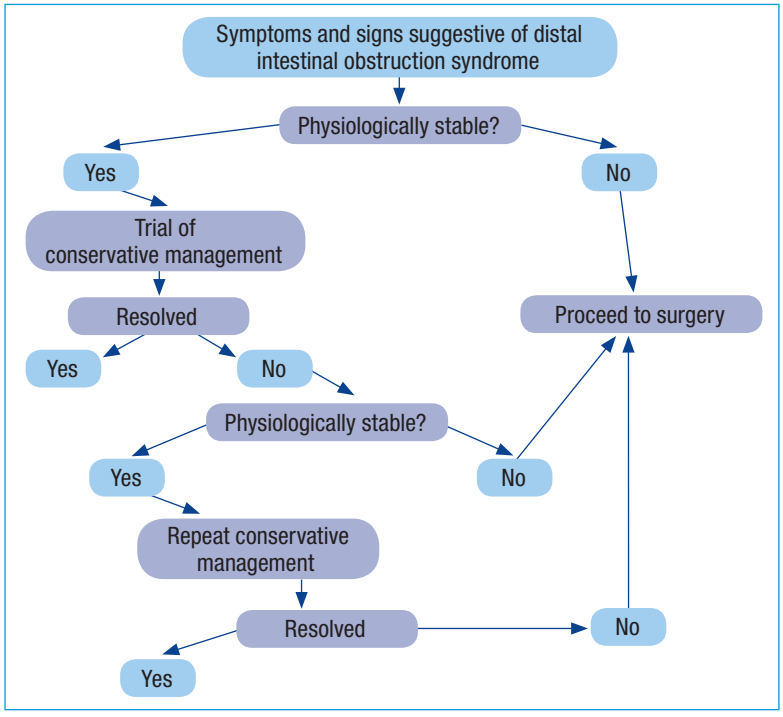
clinical symptoms. This is a small sample size but since this study others have shown good effects using a variety of gastrografin enemas, polyethylene glycol, gastrografin lavage or a combination of polyethylene glycol and gastrografin lavage. Jackson and Raiji (2011) reported a 40–70% resolution with conservative management and most retrospective studies seem to support this with Escobar et al (2005) reporting a 77.8% resolution and Farrelly et al (2014) 71%. In patients with incomplete distal intestinal obstruction syndrome and those with complete distal intestinal obstruction syndrome but not in extremis, a trial of conservative treatment is certainly warranted in the first instance.

Surgery

Surgical intervention is necessary in patients with severe distal intestinal obstruction syndrome in whom conservative management has failed to achieve a satisfactory resolution or in whom there is significant physiological derangement. Various studies have examined the incidence of surgical intervention, quoting rates ranging from 8–35% of patients (Escobar et al, 2005; Farrelly et al, 2014; Subhi et al, 2014). A range of options is available surgically depending upon the findings at laparotomy. Farrelly et al (2014) looked at the differing surgical procedures carried out across a 20-year period. They reported that the majority of patients who were treated surgically were successfully treated with enterotomy and washout or with a small bowel resection with primary anastomosis. Only one required formal right hemicolectomy and three resulted in the formation of an ileostomy from a total of 14 operative episodes in 10 patients. All cases involved extensive adhesiolysis and all had had previous surgery for meconium ileus. Similarly in the series presented by Minkes et al (1999) only two of seven patients required an ileostomy, the rest were treated with enterotomies and primary closure and one with a small bowel resection and primary anastomosis. Likewise in the review presented by Escobar et al (2005) only one patient required an ileostomy, the rest being treated with enterotomies or resection with primary anastomosis.

The evidence indicates that distal intestinal obstruction syndrome should be managed in a stepwise fashion. All patients if clinically suitable should have a trial of conservative management as in many cases this is sufficient. Even in recurrent episodes it is advisable to retry conservative management initially as this has been of benefit. Surgery is indicated when conservative management has failed and there is progression of symptoms without relief. In surgical management the least invasive procedure should be sought. As outlined above, an enterotomy with primary anastomosis may be all that is necessary to bring about resolution. Based on the evidence the authors propose the following stepwise pathway for managing distal intestinal obstruction syndrome. Obviously this is a guideline and individual cases will have exceptions but the authors propose that provided the patient remains physiologically stable an initial trial of conservative management would be prudent. If the obstruction is not resolving and the patient still remains physiologically stable then it would not be unreasonable to repeat another trial of conservative management. However, if at any point the patient becomes unstable or the obstruction is progressing without resolution via conservative management then surgical intervention is indicated. This is likely to involve laparotomy with adhesiolysis plus a procedure to relieve the obstruction, usually milking the plug and an enterotomy to remove it. Some circumstances may need a more involved procedure such as a right hemicolectomy. One article has reported the use of hand-assisted laparoscopy to relieve the obstruction but this has not been widely reported and laparoscopy may be limited by the extent of the obstruction (Abicht et al, 2012). The authors' pathway is outlined in *Figure 1*.

Figure 1. Flowchart showing recommended management of distal intestinal obstruction syndrome distal intestinal obstruction syndrome.



Prevention

Recurrent episodes of distal intestinal obstruction syndrome are well documented, for example Dray et al (2004) reported that of 27 episodes of distal intestinal obstruction syndrome studied, 13 were recurrent episodes. Decreasing the modifiable risk factors is undertaken to try and prevent further episodes. Prophylactic doses of laxatives have been advised to promote bowel transit (Colombo et al, 2011). This seems a logical step but no supportive evidence has been found.

Increasing the dosage of pancreatic supplements is a controversial topic. It has been hypothesized that insufficient levels of pancreatic supplements may lead to an increased rate of distal intestinal obstruction syndrome, a hypothesis that seems logical given that the majority

of patients presenting with distal intestinal obstruction syndrome suffer from pancreatic insufficiency. However, Rosenstein and Langbaum (1983) found no significant difference in rates of distal intestinal obstruction syndrome between patients taking varying levels of pancreatic supplements. Furthermore higher dosages of pancreatic enzyme supplementations cause other colonic complications such as fibrosing colonopathy (Smyth et al, 1994).

Other pathologies

Abdominal pain is a common symptom in patients with cystic fibrosis. Various other colonic pathologies affect people with cystic fibrosis and present similarly to distal intestinal obstruction syndrome. These are important to consider in order to make an accurate diagnosis and initiate the appropriate treatment.

Fibrosing colonopathy

The first reports of fibrosing colonopathy appeared in the literature in 1994 (Smyth et al, 1994). It was described as presenting with features of distal intestinal obstruction but there was a failure of resolution with conservative management. At surgery patients were found to have developed dense colonic strictures. The only linking features between these patients was that about a year before presentation they had all been converted to high dose pancreatic enzyme replacement therapy (Oades et al, 1994; Smyth et al, 1994). The exact pathophysiology of fibrosing colonopathy has not been identified but multiple case reports have been published associating fibrosing colonopathy with high dose pancreatic enzyme replacement, and a case-control study of 29 cystic fibrosis patients with fibrosing colonopathy showed a greatly increased relative risk for developing fibrosing colonopathy in those taking higher dose pancreatic enzyme replacements (FitzSimmons et al, 1997). Despite this the link remains casual and more formal evidence has not been published. Littlewood et al (2006) looked at 64 patients with cystic fibrosis taking high dose pancreatic enzyme replacement therapy (Creon 40 000) over a 2-year period and none developed fibrosing colonopathy.

The presentation of fibrosing colonopathy is much the same as distal intestinal obstruction syndrome, although conservative management tends to be unhelpful. Barium and gastrograffin studies may show evidence of colonic strictures (Smyth, 1996). Ultrasound and abdominal radiographs may also show evidence of colonic wall thickening. However, despite all of this fibrosing colonopathy is a histopathological diagnosis and this requires either a specimen resected intraoperatively or a full thickness colonic biopsy (Smyth, 1996). The histopathological findings are of submucosal fibrosis along with thickening of the muscularis propria and mucosal layers. There is also moderate to severe infiltration of eosinophils within the colonic wall (Pawel et al, 1997).

Appendicitis in cystic fibrosis patients

Appendicitis is the condition most often confused with distal intestinal obstruction syndrome. The incidence of appendicitis is estimated to be 1–2% of people with cystic fibrosis, considerably lower than the 7% quoted for the general population (Shields et al, 1991). The presentation of right iliac fossa pain and swelling is similar to that of distal intestinal obstruction syndrome and the development of an appendicular abscess or mass can contribute to this confusion. Appendicular abscess formation or perforations are more commonly seen in patients with cystic fibrosis. This is hypothesized to be the result of a longer period to presentation owing to recurrent bouts of colicky abdominal pain commonly seen in patients with cystic fibrosis (Al Abed et al, 2007). In addition further appendicular complications have been reported in patients with cystic fibrosis, including appendico-colic and appendicitis-cutaneous fistulae, also thought to be the result of the length of time to diagnosis (Rogers et al, 2004; Morris-Stiff and Islam, 2010). Moreover radiological diagnosis can be difficult because of the mucous distension of the appendix in patients with cystic fibrosis (Lardenoye et al, 2004). This can also be confusing in any proceeding surgical procedure.

Intussusception

Intussusception is a well-documented pathology in infancy. Its appearance after this time is not unheard of but is more prevalent in people who have cystic fibrosis. The aetiology of this has not been fully identified but it is hypothesized that the increased viscosity of the stool as a result of increased mucous secretion may have a role to play (Robertson et al, 2006). Intussusception may present with features similar to distal intestinal obstruction syndrome, with abdominal distension and a palpable intra-abdominal mass. It is an important differential diagnosis to exclude to ensure prompt and proper management, and computed tomography may have a role in making this important distinction.

Intestinal malignancy

As treatments for cystic fibrosis improve and patients survive longer, cases of intestinal malignancy have begun to be reported more commonly. In the presentation of acute obstruction and a palpable abdominal mass in the older patient with cystic fibrosis the diagnosis of malignancy is an important consideration (Robertson et al, 2006). Again computed tomography is very helpful in establishing this diagnosis.

Future research

The future of distal intestinal obstruction syndrome management will be in the use of minimal access surgery. The authors believe that as laparoscopic skills continue to improve laparoscopy will replace laparotomy as the first line of surgical management. However, open surgery will remain as the last bastion for patients who have dense adhesions from recurrent episodes of distal intestinal obstruction syndrome or meconium ileus.

Conclusions

Distal intestinal obstruction syndrome is an important abdominal manifestation of cystic fibrosis to be aware of. It is important not only for those working in tertiary paediatric and cystic fibrosis units but also for general physicians and surgeons in smaller district general hospitals. It is important to consider that various other colonic and intestinal pathologies can present in similar ways in patients with cystic fibrosis. Prompt diagnosis is essential to ensure that the correct and most efficacious management is provided. In the management of distal intestinal obstruction syndrome a conservative, less invasive approach should be considered first in suitable patients, as most episodes will resolve with this management. Recurrent episodes occur and it should be considered in patients with cystic fibrosis presenting with recurrent episodes of abdominal pain and obstruction, keeping in mind that distal intestinal obstruction syndrome may be complete or incomplete. It is an important condition to consider in the differential of the patient with cystic fibrosis presenting with right iliac fossa tenderness and signs of obstruction. **BJHM**

Conflict of interest: none.

KEY POINTS

- Distal intestinal obstruction syndrome is a common complication of cystic fibrosis occurring in 10–24% of patients; the clinical features are pain, abdominal distension, bloating and vomiting.
- Other pathologies cause similar symptoms and early diagnosis is essential to provide prompt treatment.
- In the management of distal intestinal obstruction syndrome use conservative management first in stable patients.
- Minimal access surgical techniques are used more and more.

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