

CURRENT TOPIC

Fibrosing colonopathy in cystic fibrosis

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In 1994, the first case reports of colonic strictures (now referred to as fibrosing colonopathy) in children with cystic fibrosis appeared in the medical literature.¹⁻⁵ The initial case reports described patients who presented with intestinal obstruction and required surgical resection of a thickened and narrowed area of colon.¹ The only aspect of these children's management that had changed was a switch to new 'high strength' pancreatic enzyme preparations about 12 months previously. It was suggested that use of these preparation may be associated with this condition. Abdominal complaints occur frequently in cystic fibrosis; for example the incidence of Crohn's disease has been reported to be 17 times higher than the general population.⁶ It was not clear initially whether these cases represented variations of the normal pathology reported in cystic fibrosis, or a new entity. In some instances, the clinical and radiological features were suggestive of Crohn's disease, or an inflammatory colitis, but the histological findings were strikingly different. It is the pathological findings (described below), not reported previously in cystic fibrosis, which have characterised this condition. I will attempt to review the clinical, radiological, and histological features of this condition and discuss the current evidence on aetiology.

Clinical features

The clinical presentation of fibrosing colonopathy is non-specific. Abdominal pain, distension, vomiting, and constipation are frequent features⁷ and have led initially to confusion with distal intestinal obstruction syndrome.⁸ However, these symptoms fail to respond to the usual medical management of distal intestinal obstruction syndrome and the patient may progress to subacute and later acute obstruction. Children have also presented with symptoms of a colitis, with diarrhoea, sometimes containing blood and mucus, abdominal pain, and anorexia.⁵ Ascites has been reported and chylous ascites has been evident in some patients at operation⁴ (R Nelson, personal communication). The reasons for this last observation are not entirely clear, although it has been suggested that there may have been obstruction of mesenteric lymphatic vessels. The onset of symptoms may be insidious, over many months, so prompt investigation of children presenting with any of these symptom complexes is clearly advisable.

The decision about when to operate may not be straightforward, except in children who have large bowel obstruction. Some children have been operated on because of intractable diarrhoea, faecal incontinence, anorexia, and weight loss.^{4,5} In a number of children who presented with evidence of extensive involvement of the colon, defunctioning ileostomies have been performed in the hope that by diverting faeces from the colon some of the changes may resolve and a more limited resection may subsequently be undertaken. The experience in some of these cases has been that rather than improving, the narrowing has progressed and become more extensive,⁷ rendering subsequent surgery more difficult. I am aware of a number of children who have presented with diffuse involvement of the colon, and in whom resection or ileostomy has been avoided. These children have remained well on conservative management. It would therefore seem wise to manage these children conservatively where possible, but with very careful clinical monitoring and annual ultrasound to assess bowel wall thickness.

Radiological features

A thickened colon wall may be evident on plain abdominal radiograph and may be confirmed by ultrasonography. The features of fibrosing colonopathy on ultrasound include bowel wall thickening of more than 2 mm,⁹ reduced peristalsis, and free fluid associated with the affected areas.¹⁰ We investigate all children who present with abdominal pain with an abdominal radiograph and bowel ultrasound. Distal intestinal obstruction syndrome is the most frequent finding.¹¹ If both are normal, then fibrosing colonopathy is very unlikely.¹² If there are any of the above abnormalities on ultrasound, then contrast studies are indicated. The findings on contrast enema fall into two main groups.¹³ In the first, the intramural widening causes a localised narrowing of the colon without mucosal abnormality. There may be evidence of obstruction. The main differential diagnosis is Crohn's disease. The second group of patients have evidence of more extensive colonic inflammation, loss of haustration, and marked mucosal abnormality. The differential diagnosis is wide and includes fibrosing colonopathy, Crohn's disease, ulcerative colitis, pseudomembranous or infective colitis.

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Pathological diagnosis

Fibrosing colonopathy is a histopathological diagnosis and requires either a resection specimen or a full thickness biopsy. Not all patients believed to have this condition have required surgery and suitable biopsy material can be obtained only by laparotomy. Colonoscopic biopsies, which usually sample the mucosa alone, are generally unsatisfactory. One is therefore left with the difficult situation of trying to identify the condition by clinical and radiological criteria. Because of the range of possible differential diagnoses, even after all imaging has been completed I believe that definitive diagnosis is not possible in such cases.

The histopathological features are pathognomonic.¹⁴ The stenoses, which are frequently long segment, result from submucosal thickening by fibrous connective tissue. This leads to intraluminal narrowing which occurs without a significant reduction in the external diameter of the colon. The epithelium is generally intact with very little inflammatory change in the affected areas.¹ In the original report of this condition the patients were described as having a localised stricture in the ascending colon, although after surgical resection, one patient subsequently developed a second stricture,¹ suggesting that the disorder may have been more widespread than originally suspected. Other reports have described patients with extensive fibrosis throughout the colon at presentation. To emphasise the long segment colonic involvement and the distinction between this condition and inflammatory strictures that are typically focal, the term fibrosing colonopathy is now used in preference to 'colonic strictures'.

Aetiology of fibrosing colonopathy

The first reports of fibrosing colonopathy and the suggested link with high strength pancreatic enzyme products came like a bombshell. Regulatory authorities moved swiftly on both sides of the Atlantic. In the UK, the Committee on Safety of Medicines recommended that patients being treated with high strength pancreatic enzyme preparations should be reviewed and unless there were special reasons they should be changed back to standard strength preparations.¹⁵ In the USA the situation was more complex. A wide range in strengths of pancreatic enzyme products was available. Because they were already on the market in the USA in 1938, before the Food Drug and Cosmetic Act, these products had not undergone the usual safety and efficacy studies.¹⁶ The Food and Drugs Administration requested withdrawal of products containing more than 20 000 units of lipase and called for standard testing of pancreatic products.¹⁷

Shortly after the first reports of fibrosing colonopathy, in the UK, epidemiological studies were designed firstly to establish the incidence of this condition in the cystic fibrosis population in the country, secondly to determine if it was a new entity, and finally to identify factors with which it was associated.¹⁴ A

cohort evaluation was initiated to address the first two of these aims. Details were requested of all cystic fibrosis patients who had undergone surgery in between 1984 and 1994. Where small or large bowel had been resected or biopsied, the histological sections were reviewed. It was well recognised that a number of cases had presented with clinical and radiological features of fibrosing colonopathy, but had not required surgery and histological material was not therefore available. Because the diagnosis in these cases was less precise, it was decided not to include them in the case-control study. Fourteen cases of fibrosing colonopathy were identified, the first occurring in April 1993. Twelve were boys and six had received some or all of their care in Liverpool. A nested case-control study was then undertaken, where each case was matched by date of birth with four controls taken from the UK cystic fibrosis survey. The case-control studied identified an association between fibrosing colonopathy and use of high strength pancreatic enzyme preparations, but not the use of low strength preparations. The association with high strength preparations was dose related, temporally credible, and biologically plausible. Not all high strength products were, however, found to be associated. Two similar products, Pancrease HL (Cilag) and Nutrizym 22 (Merck) were found to be associated with fibrosing colonopathy, but Creon 25000 (Duphar) was not.

The study also demonstrated that cases were more likely than controls to have taken laxatives in the 12 months before surgery. A possible explanation for this was that when patients with fibrosing colonopathy initially presented they had abdominal pain. Some were thought to have distal intestinal obstruction syndrome and were therefore treated with laxatives. This illustrates the difficulty of inferring causality on the basis of an association demonstrated in an observational case-control study.

There were two main hypotheses generated from this case-control study. The first was that the disorder is due to one of the active constituents of pancreatic enzyme preparations. The use of high strength enzyme preparations would enable much larger doses of such an active constituent to be delivered to the colon. If this hypothesis were correct, this condition may occur if sufficiently large doses of low strength preparations were taken. An alternative hypothesis is that the disorder is due to an excipient present in the enteric coating of the microencapsulated preparations, which damages the colon in a dose dependent manner. Creon 35000 is formulated as microspheres, which are heterogenous in size; Pancrease HL and Nutrizym 22 are formulated as minitables which are of uniform size. Eudragit-L, one of the components of the minitab coating, is a copolymer based on methylacrylic acid and ethyl acrylate. These compounds have been shown to have a toxic effect on the gut of experimental animals.^{18 19} It has been suggested that the methylacrylic acid copolymer present in the enteric coating

of some preparations may be causal factor in the aetiology of fibrosing colonopathy.²⁰ This hypothesis would explain the association with high strength preparations, and the difference in association between different high strength products. Indirect evidence in support of the second hypothesis has come from two further observations. The first is that two, histologically confirmed, cases of fibrosing colonopathy have been described in young children treated with the low strength preparation Nutrizym GR (Merck).^{20 21} Nutrizym GR is one of the few low strength preparations that contains the methylacrylic acid copolymer.²⁰ The second observation was reported recently by Croft *et al*, who used the technique of whole gut lavage to study gut inflammation in patients with cystic fibrosis receiving high strength pancreatic enzyme preparations.²² They found that two patients, who were both taking Nutrizym 22, had strikingly abnormal results indicative of severe mucosal inflammation.

Clearly there is still uncertainty about the aetiology of fibrosing colonopathy and further work is needed to investigate both of the hypotheses described above. The Committee on Safety of Medicines has considered the results of the case-control study and has recommended that Pancrease HL and Nutrizym 22 are not used in children under the age of 15 years. They have also suggested that it would be prudent to avoid total daily doses of enzyme supplementation above 10 000 units of lipase/kilogram/day.²³ In the USA, a recent consensus committee has made similar recommendations, advocating a maximum dose of 2500 units of lipase/kilogram/meal.²⁴

Conclusion

The introduction of enteric coated pancreatic enzyme supplements in the early 1980s was undoubtedly one of the major advances in the care of children with cystic fibrosis. Further refinements in the presentation of these preparations inevitably followed, to improve patient acceptability and compliance. The emergence of fibrosing colonopathy took clinicians dealing with cystic fibrosis completely by surprise, and in the last two years there has been a gradual appreciation that as far as pancreatic enzyme products are concerned 'More is not necessarily better'.¹⁶ However, it is encouraging that, in the UK, there have been no histologically confirmed cases in children receiving high strength pancreatic enzyme preparations since July 1994. Hopefully this trend will continue and the causal factors will be defined, ensuring that this serious complication can be effectively prevented in the future.

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Commentary

Implications of the Committee on Safety of Medicines 10 000 IU lipase/kg/day recommendation for use of pancreatic enzymes in cystic fibrosis

The latest recommendation of the Committee on Safety of Medicines that 'it would be prudent to avoid doses of pancreatic enzyme supplements in excess of 10 000 units of lipase/kg/day, irrespective of the preparation' has caused a problem for paediatricians who have cystic fibrosis patients, many of whom are taking considerably more enzymes than recommended. Most patients have reached their present dose by increasing the number of enzymes to a level sufficient to control their gastrointestinal symptoms and signs. In some patients the symptoms may not have been caused by their intestinal malabsorption and the increase in dose is inappropriate and results in their taking an excessive dose of enzymes. However, there are many others who certainly do require more than the recommended 10 000 units of lipase/kg/day to control both their symptoms and their fat malabsorption. Unfortunately both must be monitored, as symptoms can occur with normal fat absorption, and severe malabsorption may occur without any symptoms.