Cows’ milk sensitive enteropathy in cystic fibrosis

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SUMMARY Proximal small intestinal mucosal biopsies were carried out in children with cystic fibrosis who had diarrhoea and failed to thrive in spite of adequate treatment, including pancreatic supplements. Histological examination of eight of the 17 biopsies taken over a period of 12 years showed evidence of enteropathy, and accounted for one in 13 (8%) children with cystic fibrosis under 3 years of age attending our clinic. Seven responded to a cows’ milk free diet; the diarrhoea stopped and weight gain increased. One of these responded only when gluten was also excluded from his diet. The eighth child remained on a normal diet and his symptoms did not improve. The enteropathy had resolved in all five patients who had further biopsies taken while receiving treatment, and from 15 months to 3 years of age all the children tolerated a normal diet and continued to thrive.

Cows’ milk sensitive enteropathy is an important cause of failure to thrive in children with cystic fibrosis. Small intestinal biopsy is an important investigation in younger children who fail to thrive and have diarrhoea despite adequate treatment.

Children with cystic fibrosis often fail to thrive. This failure is usually related to the disease itself, and may be the result of recurrent chest infections, inadequate food, or pancreatic enzyme deficiency. Two gastrointestinal diseases that may, in association with cystic fibrosis, cause failure to thrive are coeliac disease and lactase deficiency.

It is important to make the correct diagnosis when a child with cystic fibrosis is failing to thrive as the severity of the respiratory component of the disease (which may affect prognosis) seems to be related to the child’s nutritional state. The aim of this study was to investigate whether cows’ milk sensitive enteropathy is a cause of chronic diarrhoea and failure to thrive in children with cystic fibrosis.

Patients and methods

Seventeen children were included in the study from 1975–1987. Fifteen of the patients were already attending the cystic fibrosis clinic and were selected for small intestinal mucosal biopsy because they were failing to thrive in spite of adequate treatment for cystic fibrosis. This included pancreatic enzyme and fat soluble vitamin supplements. Two other children underwent small intestinal mucosal biopsy and sweat tests during the same admission as part of the routine procedure for investigation of failure to thrive, and had positive sweat tests. They were taking no medication at the time of biopsy. The weights of all the children were below the 25th percentile, and five were well below the third.

Nine of the children were boys and eight girls. They were aged from 3 months to 12 years (median 12 months). In all cases the diagnosis of cystic fibrosis was made from two positive sweat tests and typical symptoms. Sweat tests were considered positive if at least 100 mg of sweat was collected that contained at least 70 mmol/l sodium.

The diagnosis of cows’ milk sensitive enteropathy was made when characteristic histological findings were present in a proximal small intestinal mucosal biopsy specimen, and there was a rapid clinical response to the exclusion of cows’ milk from the diet. Early challenge with cows’ milk and further small intestinal biopsies were necessary to prove that the disease was present. In practice, as the condition was a temporary one and there was a risk of anaphylaxis on the reintroduction of cows’ milk, challenge was not considered necessary if the histology was characteristic and the clinical improvement rapid.

At the time of small intestinal mucosal biopsy, 16 of the children were on cows’ milk based feeds, and one was breast fed. The mother of the latter child included cows’ milk in her diet. Three children under 6 months old were on full fat adapted formula feeds, three were taking ‘cystic mix’ (SMA and
Marvel with added Caloreen), and the other 10 were having skimmed milk. The 13 oldest children included a normal amount of gluten in their diets, but the four youngest had not started solids. Stool samples were taken from all patients and examined for pathogens. The small intestinal mucosal biopsy specimens were taken after full informed consent had been given by the parents.

After an overnight fast, a paediatric sized double port capsule was used to obtain mucosa from the duodenojejunal flexure under radiological control. In addition to the biopsy specimen, duodenal juice was aspirated if possible and examined for the presence of Giardia lamblia. A sample of tissue from one biopsy specimen from each patient was frozen in liquid nitrogen and used to assay disaccharidases, and the other was fixed in formal saline and processed for histological examination. Suitable specimens were also analysed morphometrically using a computer based image analysis system. If the histological appearance of a biopsy was abnormal and consistent with a cows' milk sensitive enteropathy, the child was given a cows' milk exclusion diet for the next few months, usually until at least 15 to 18 months of age. These children were reviewed regularly in the outpatient clinic with particular attention being paid to weight gain and stool frequency. If possible proximal small intestinal mucosal biopsy was repeated before cows' milk was reintroduced to their diets. Morphometric analysis of the biopsy specimens was again performed and the results were compared with those of the specimens obtained on presentation.

Other features of the children with enteropathies that were reviewed were: the manner of initial presentation with cystic fibrosis; a personal or family history of atopy; and any investigations which might have indicated an atopic tendency. These included examination of peripheral blood for eosinophils, skin prick tests for allergens, and estimation of serum IgE and specific IgE concentrations. Sixteen per cent of all children attending our clinic during the 12 year period presented with meconium ileus.

**Results**

In nine of the 17 children proximal small intestinal biopsy specimens were histologically normal. They were aged from 3 months to 12 years (median 2 years). Seven were girls and two boys. No pathogenic organisms were detected in their stool samples, and G lamblia was not detected in any duodenal aspirate. No gastrointestinal cause other than cystic fibrosis was found to explain their failure to thrive and chronic diarrhoea.

Histological and morphometric findings in the biopsy specimens from the remaining eight children were abnormal and consistent with cows' milk sensitive enteropathy—that is, they had thin mucosa with reduced villous height (fig 1). Seven of these children were boys, and their ages ranged from 5 months to 28 months (median 10). This group included one of the children who underwent small intestinal mucosal biopsy at the same time as cystic fibrosis was diagnosed. Rotavirus was detected by electron microscopy both in the stool and within the small intestinal mucosa of one child. No pathogens were detected in stool or duodenal aspirate from any other patient.

The child with most frequent diarrhoea (10 times a day) had an enteropathy, while the child without diarrhoea did not. Apart from these two cases, there was no obvious difference in stool output between those children with enteropathy and those with normal small intestinal mucosa.

Patients with enteropathy were on a variety of cows' milk based feeds. Three were on formula feeds, two were on cystic mix, one was on doorstep milk, and the other two on skimmed milk.

Four of the eight children with enteropathy had originally presented with meconium ileus, whereas about 16% of all children attending the clinic over the 12 years had presented in this manner. The other four had presented with failure to thrive, and one also had recurrent chest infections. At the time of small intestinal mucosal biopsy the weights of five were below the third percentile (and the other three on or below the 10th), all their birth weights had

**Fig 1** Morphometric findings in patients with and without cows' milk sensitive enteropathy. Dots represent the 13 patients studied, and vertical bars the findings of Maluenda et al (mean (SD)).
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been in the normal range. All seven available for follow up had developed atopic symptoms, which included asthma in five, eczema in two, and urticaria in one. Three children had appreciable eosinophilia (more than 400 × 10^6/l) on at least one occasion.

Disaccharidase activities were normal in the four histologically normal biopsy specimens in which they were measured. Sucrase and maltase activities were normal in the six children with enteropathy in which they were measured. Lactase activity was reduced in two (0.5 and 0.8 mmol/min/g). This was not associated with clinical lactose intolerance in either child.

Seven of the eight children with small bowel mucosal abnormalities compatible with the diagnosis of cows’ milk sensitive enteropathy had cows’ milk withdrawn from their diets; Pregestimil was used as a substitute feed. The diagnosis does not seem to have been considered in one child who was biopsied in 1976, who remained on cows’ milk, and who continued to fail to thrive. He died from a chest infection aged 3 years.

In six of the seven children stool consistency improved, stool frequency fell to two or three times a day, and they had ‘catch up’ weight gain. One child whose weight on presentation was well below the third percentile (3.6 kg at 6 months) almost reached this percentile in six months. One child’s weight climbed from the third to the 10th percentile, two from the tenth to the 25th, and two reached the 50th percentile (one from the third and the other from the 10th).

The one child who did not improve rapidly underwent a further proximal small intestinal biopsy, which showed that enteropathy was still present. Gluten was excluded from his diet in addition to cows’ milk, and a third biopsy showed improvement in the histological picture. He underwent two further biopsies, both of which were normal. The first was at 3 years of age after cows’ milk was reintroduced to his diet, and the other at 4 years of age when his diet also included gluten, so he had transient gluten intolerance rather than coeliac disease.

Small intestinal biopsy was also repeated in four of the seven other children with enteropathy 2–14 months later while they were receiving cows’ milk free diets. Reasons for not repeating the biopsy in the other three were: adverse social circumstances (n=1), follow up continued elsewhere (n=1), and cows’ milk sensitive enteropathy not recognised (n=1). All five biopsy specimens showed obvious improvement on histological examination.

Four of the five specimens were suitable for morphometric analysis. Fig 2 shows the results of morphometry in these, and compares them with the morphometric findings on presentation. In four the mucosal thickness improved, and in all cases the ratio of villous height:crypt zone depth improved.

Disaccharidase activities were again measured, and the child who had had the lowest lactase activity now had one within the normal range (1–8).

The children were challenged with cows’ milk from 2–13 months (median 10 months) after excluding it from their diets. There were no adverse reactions, weight gain continued at the same rate as previously, and stool frequency was unchanged.

**Discussion**

Cows’ milk sensitive enteropathy was a common problem among the children under 3 years old (8/13, 62%) who were selected from our cystic fibrosis clinic for small intestinal mucosal biopsy. As 105 children had presented to our clinic by 3 years of age from 1975–87, the overall incidence of the enteropathy in children presenting with cystic fibrosis in this age group was 1/13. The incidence of cows’ milk sensitive enteropathy in the general population is difficult to establish, particularly as so many children are started on restricted diets without seeing a doctor, but it seems to be considerably lower than this.9

Three possible reasons for a high incidence in children with cystic fibrosis are: the association of cystic fibrosis with atopy10 (cows’ milk sensitive enteropathy is an atopic related disorder), increased intestinal permeability,11 and impaired digestion of protein due to insufficient pancreatic trypsin leading to a high antigen load presenting to the small intestinal mucosa.
The main features of this group of patients were the unequal sex ratio, the high incidence of atopy, and the presentation with meconium ileus. A predominance of boys with a family history of atopy has previously been reported in a group of children presenting with cows' milk sensitivity.\textsuperscript{12} Atopic symptoms are common in children with cows' milk sensitive enteropathy alone,\textsuperscript{13} and as already mentioned atopy is associated with cystic fibrosis.\textsuperscript{10} The incidence of meconium ileus would of course be higher in this group than among all children with cystic fibrosis, as cows' milk sensitive enteropathy is a disease of infancy, and many children with cystic fibrosis present later. The incidence of 50\% is surprisingly high, however, when the overall incidence in our clinic was 16\%.

In some cases, although the mucosal appearance had improved when cows' milk was excluded from the diet, it was not entirely normal. This is similar to previous findings\textsuperscript{6} and could indicate that in spite of advice from a dietitian these children may have continued to ingest some cows' milk. Alternatively they may have reacted to Pregestimil or other dietary constituents, although this was not clinically apparent. One child was intolerant of gluten, which illustrates the fact that multiple food intolerances may co-exist.\textsuperscript{14} It was because of this that Pregestimil was used as a cows' milk substitute (rather than a soya based milk), because at least 15\% of children intolerant of cows' milk also react to soya milk.\textsuperscript{7} As all the children treated for cows' milk sensitive enteropathy were given Pregestimil feeds, there were no 'control' children. It could be argued that children with cystic fibrosis, even without cows' milk sensitive enteropathy, would thrive better on Pregestimil than cows' milk feeds because Pregestimil contains fat in the form of medium chain triglycerides which are water miscible and more rapidly hydrolysed by pancreatic lipase than long chain triglycerides. Cows' milk feeds, however, do have the advantages of higher salt and protein contents. When our group of children were restarted on diets containing cows' milk there were no noticeable changes in the rate of weight gain, so there was no evidence that either milk was superior once tolerance to cows' milk had been achieved.

Although cases of cows' milk sensitive enteropathy in patients with cystic fibrosis do not seem to have been reported previously, the enteropathy may have been described.\textsuperscript{4 15 16} Antonowicz \textit{et al} reported 27 cases of cystic fibrosis with steatorrhoea in association with small bowel enteropathy; no explanation for the enteropathies was given.\textsuperscript{4} Reduction in disaccharidase activities was thought to be secondary to the partial villous atrophy (as in our two cases with low activities of lactase on presenta-

\textbf{References}

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