CONTROVERSY

The value of proximal small intestinal biopsy in the differential diagnosis of chronic diarrhoea

A G Thomas, A D Phillips, J A Walker-Smith

Abstract

The value of proximal intestinal mucosal biopsy was reviewed in 381 children presenting with chronic diarrhoea over an eight year period. An enteropathy was detected in 44% of cases and was more frequently seen in those aged less than 6 months. A diagnosis was established in 91% of cases. The most common diagnosis was the postenteritis syndrome where the presence of an enteropathy indicated those requiring treatment with a cows' milk free diet. Other conditions where a biopsy facilitated diagnosis or treatment included giardiasis, enteropathogenic *Escheriichia coli*, crytosporidiosis, autoimmune enteropathy, and microvillous atrophy.

Coeliac disease was considered in 55% of children and established in 8%, clearly identifying those requiring a gluten free diet. This also emphasises the important role of the biopsy procedure in the exclusion of specific diseases.

Proximal small intestinal mucosal biopsy is an essential investigation in children with chronic diarrhoea in whom an enteropathy is suspected.

Diarrhoea is a major cause of morbidity and mortality in children throughout the world.[1] The advent of oral rehydration therapy represents a major advance in the management of acute diarrhoea.[2–4] However, this does not resolve the problem of chronic diarrhoea, which represents a difficult diagnostic problem because of the many causes that can be considered to be responsible for the illness.[5] The approach at Queen Elizabeth Hospital for Children is to perform a proximal small intestinal mucosal biopsy as a differential diagnostic procedure in children with chronic diarrhoea in whom an enteropathy is suspected. The aim of this paper is to assess the value of such an approach.

Queen Elizabeth Hospital for Children, Hackney Road, London E2 8PS, Academic Department of Paediatric Gastroenterology
A G Thomas
J A Walker-Smith

Electron Microscopy Department
A D Phillips

Correspondence to:
Dr Phillips.

Patients and methods

The patients reviewed in the study were those presenting at Queen Elizabeth Hospital for Children between January 1982 and December 1989 with chronic diarrhoea (duration at least 14 days) who underwent proximal small intestinal mucosal biopsy.

The investigative procedure for these patients included an initial clinical assessment followed by routine microbiological, haematological, and biochemical analyses. Microbiological examination of the stools comprised negative staining electron microscopy for gastrointestinal viruses and light microscopy for ovas, cysts, and parasites. Bacterial culture was performed in order to identify salmonella, *Escherichia coli*, and shigella. After obtaining informed consent the children were fasted overnight, sedated, and a proximal small intestinal mucosal biopsy specimen obtained using a paediatric twin port biopsy capsule.[6] Histology, morphometry,[7] biochemistry,[8] and ultrastructure[9] of the small intestinal mucosa were studied depending on the specific clinical requirements. Duodenal juice was examined for the presence of *Giardia lamblia*. The histological report for each biopsy specimen was reviewed and, for the purposes of this study, graded into normal histology and mild, moderate, or severe enteropathy.[10] This grading depends mainly on the villous height and crypt depth. Discrete abnormalities such as those associated with lymphangiectasia were included in the normal group as the villous height and crypt depth were normal.

Patients with cows' milk sensitive enteropathy and postenteritis enteropathy were considered together as the diseases may coexist and are difficult to separate without resorting to food provocation and serial small intestinal biopsies.[11]

Results

During the eight year period 414 children presented with chronic diarrhoea and underwent proximal small intestinal mucosal biopsy. The notes of 381 were retrieved and reviewed retrospectively.

Two hundred and forty two of the patients (64%) were aged less than 2 years, 78 (20%) were between 2 and 5 years old, and the remainder (n=61, 16%) ranged up to 15 years of age. The male to female ratio was 1·4 : 1 (223 : 158). Coeliac disease was considered as part of the differential diagnosis in 210 of the children.

Two hundred and twelve children (56%) had a normal villous height and crypt depth (fig 1); 169 (44%) had an enteropathy, which was mild in 97 (25%) (fig 2), moderate in 38 (10%) (fig 3), and severe in 34 (9%) (fig 4). Enteropathy was more frequent ($p<0·01$) in those aged <6 months (occurring in 76% 41/54) and less frequent ($p<0·01$) in those aged more than 5 years (occurring in 25%, 16/61); analyses by χ^2 test.

In the group with normal histology (fig 1)

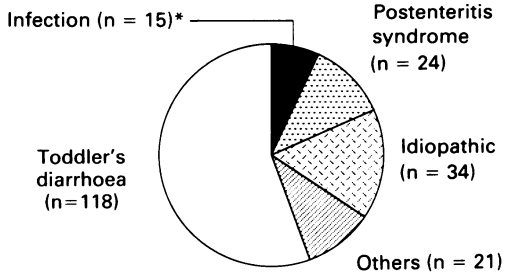

*Figure 1 Diagnoses of 212 children with normal histology. *For the 15 children with infection the infecting organisms were: salmonella (n=2), G lamblia (n=5), enteropathogenic E coli (n=4), aeromonas (n=3), and campylobacter (n=1).*

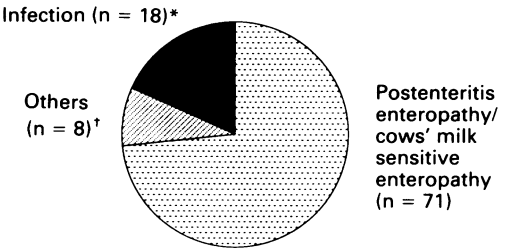

*Figure 2 Diagnoses of 97 children with mild enteropathy. *For the 18 children with infection the infecting organisms were: G lamblia (n=5), cryptosporidium (n=5) cryptosporidium + G lamblia (n=1) enteropathogenic E coli (n=4), campylobacter (n=1), and mixed bacteria (n=2). †The other eight children had inflammatory bowel disease (n=3), coeliac disease (n=2), intractable diarrhoea of infancy (n=2), and idiopathic intestinal pseudo-obstruction (n=1).*

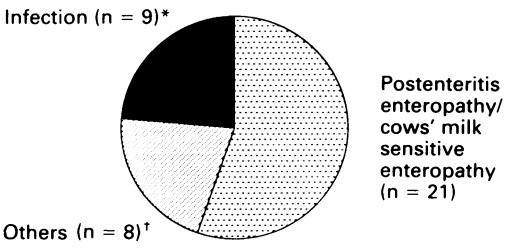

*Figure 3 Diagnoses of 38 children with moderate enteropathy. *For the nine children with infection the infecting organisms were: G lamblia (n=5), cryptosporidium (n=2), enteropathogenic E coli (n=1), and mixed bacteria (n=1). †The other eight children had intractable diarrhoea of infancy (n=2), autoimmune enteropathy (n=2), inflammatory bowel disease (n=1), allergic enteropathy (n=1), coeliac disease (n=1), and congenital microvillous atrophy (n=1).*

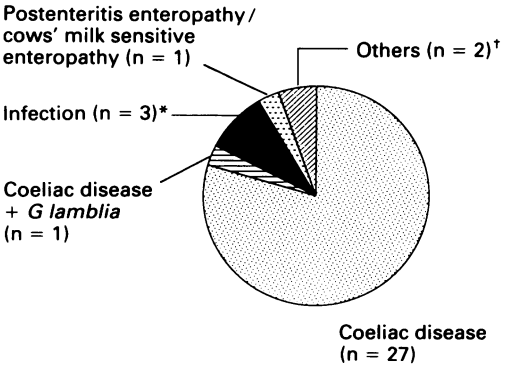

*Figure 4 Diagnoses of 34 children with severe enteropathy. *The infecting organism for all three children was G lamblia. †The other two children had intractable diarrhoea (n=1) and autoimmune enteropathy.*

toddler's diarrhoea was the commonest diagnosis (118/212, 56%). Twenty four cases (11%) were associated with the postenteritis syndrome, that is acute onset of diarrhoea persisting for more than 14 days, with or without failure to thrive. Of these 23 (96%) remained on a normal diet with spontaneous resolution of diarrhoea. In 15 patients (7%) bacteria or parasites were demonstrated. Other diagnoses were: food allergy (n=4), cystic fibrosis (n=3), IgA deficiency (n=3), sucrase-isomaltase deficiency (n=2), secondary lactase deficiency (n=2), glucose-galactase malabsorption (n=1), lymphangiectasia (n=1), ileal stricture (n=1), Shwachman's syndrome (n=1), nodular lymphoid hyperplasia (n=1), eosinophilic gastroenteritis (n=1), and inflammatory bowel disease (n=1). No diagnosis was established in 34 children with a normal mucosa (16% or normal histology group, 9% of total cases).

Postenteritis enteropathy or cows' milk sensitive enteropathy was the commonest diagnosis associated with mild histological changes (n=71, 73%; fig 2). In 18 (19%) cases pathogens, including *G lamblia*, cryptosporidium, campylobacter, and enteropathogenic *E coli*, were demonstrated. Other diagnoses included coeliac disease, inflammatory bowel disease, and idiopathic intractable diarrhoea of infancy. The patients with coeliac disease were biopsied on gluten challenge in order to establish the diagnosis after an empirical trial of a gluten free diet at another hospital.

Postenteritis enteropathy or cows' milk sensitive enteropathy was also the commonest diagnosis associated with moderate histological changes (n=21, 55%; fig 3). In nine (24%) cases pathogens were demonstrated and in eight (21%) cases other causes were established.

Severe enteropathy was associated with coeliac disease in 27/34 cases (79%), giardiasis in three (9%), and coeliac disease with giardiasis in one (3%). Other diagnoses included autoimmune enteropathy, the intractable diarrhoea of infancy syndrome, and the postenteritis syndrome (fig 4).

A total of 20 cases of giardiasis were identified. In 14 cases the parasite was identified by light microscopical examination of duodenal juice and/or small intestinal mucosa and was not seen in stool samples. In three cases giardia was found only in stool samples.

Discussion

Proximal small intestinal mucosal biopsy affords the demonstration of diffuse, but not discrete, abnormalities,[12] and in this series 44% of cases had an enteropathy identified. This alone serves to indicate its importance in paediatric gastroenterology. Its practical value resides not only in its ability to provide differential diagnostic information (when used in conjunction with clinical and laboratory procedures), but also to exclude diagnoses. For example, a diagnosis of toddler's diarrhoea is generally reached on clinical grounds.[13] However, the patients described here (representing a minority of the total referrals with toddler's diarrhoea during the study period) were suspected of having an

enteropathy due to coeliac disease or cows' milk protein intolerance. After the demonstration of a normal small intestinal mucosa on a normal diet the diagnoses associated with the presence of an enteropathy were excluded. Similarly although no cause was found to explain the symptoms in 9% of cases, the biopsy procedure allowed many gastrointestinal diseases to be excluded.

A diagnosis was established in 91% of cases. The commonest diagnosis was the postenteritis syndrome in 117 (31%). In 24 children a normal mucosa was demonstrated and 23 were continued on a normal diet with resolution of the diarrhoea—that is, the biopsy influenced management with a successful outcome in all but one case. Seventy patients had mild, 21 had moderate, and one had severe histological changes. These children were placed on cows' milk free diets with immediate clinical benefit and several months later a carefully controlled milk challenge was performed in hospital. Most cases were able to tolerate a milk containing diet by the age of 2 years. Thus, the presence or absence of histological changes has helped to indicate which patients with the postenteritis syndrome require treatment with a milk free diet.

In 46 cases pathogens were demonstrated. *G lamblia* was identified in 20 (43%) and indicated treatment with metronidazole. Proximal small intestinal mucosal biopsy was a more effective method for the detection of *G lamblia* than stool microscopy.[14] One patient who did not improve after metronidazole treatment had further biopsies that established the additional diagnosis of coeliac disease. This underlines the value of the procedure in the differential diagnosis of chronic diarrhoea.

Enteropathogenic *E coli*, when identified adhering to the mucosa, were treated with appropriate antibiotics.[15] The finding of cryptosporidium explained the presence of an enteropathy[16] and indicated that therapeutic intervention would be ineffective. In all cases the diarrhoea resolved spontaneously.

Only 8% of the patients coming to biopsy had coeliac disease, even though it was considered as part of the differential diagnosis in the majority of cases. Thus a major role of the biopsy procedure is to exclude the presence of coeliac disease and thereby avoid the pitfalls of empirical treatment. As treatment of coeliac disease is for life it is crucial that the diagnosis is substantiated.

Other diagnoses associated with a severe enteropathy included autoimmune enteropathy,[17] congenital microvillous atrophy,[18] and the idiopathic intractable diarrhoea of infancy syndrome. A small intestinal biopsy is required for the diagnosis of microvillous atrophy and has allowed this discrete disorder to be recognised as part of the differential diagnosis of the intractable diarrhoea of infancy syndrome,[18] along with autoimmune enteropathy.[17] Indeed, proximal small intestinal biopsy has facilitated the evaluation of therapeutic trials in these diseases.[19–21]

In conclusion, we have reviewed the use of proximal small intestinal mucosal biopsy in children presenting with chronic diarrhoea. The routine performance of this procedure has established different diagnoses within the umbrella of chronic diarrhoea and influences management.[15–18] In experienced hands it is a simple and safe procedure and is an essential investigation in chronic diarrhoea.

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Commentary

This paper comes from a department which has set standards for paediatric gastroenterologists so its conclusions must be treated with respect. Children with diarrhoea lasting more than 14 days, in whom an enteropathy was suspected, underwent small intestinal mucosal biopsy. The authors conclude that this investigative technique is *essential* in such children.

Apart from providing an interesting insight into the spectrum of chronic diarrhoeal disease as experienced in east London, what message does this paper hold for general practitioners and general paediatricians who, elsewhere in the country, treat the bulk of such patients?