Investigating inflammatory bowel disease – white cell scanning, radiology, and colonoscopy

J C Jobling, K J Lindley, Y Yousef, I Gordon, P J Milla

Abstract

Objective—To evaluate different methods of examination of the bowel in suspected inflammatory bowel disease.

Design—Prospective investigation of all children over a three year period with suspected inflammatory bowel disease. A technetium-99m-HMPAO labelled white cell scan (Tc-WCS), barium follow through examination (Ba-FT), and colonoscopy plus biopsy were undertaken.

Setting—Great Ormond Street Hospital for Children, London.

Subjects—39 children (20 male and 19 female), median age 12.1 years (range 3.9–15.1 years).

Main outcome measures—There was total agreement in 21/39 cases, positive in 16, and negative in five. Of 31 histologically proved cases, positive results were obtained in 28 Tc-WCSs (sensitivity 90%), 10 of 24 Ba-FTs (sensitivity 42%), and 27 colonoscopies (sensitivity 87%).

Conclusion—The Tc-WCS is sensitive, specific, and non-invasive and should be a first line investigation. Ba-FT with a high radiation burden and relatively low sensitivity requires its role to be redefined. Colonoscopy, with endoscopic biopsy, has a high pick-up rate where facilities and expertise exist.

(Arch Dis Child 1996; 74: 22–26)

Keywords: inflammatory bowel disease diagnosis, Tc-HMPAO, colonoscopy.

The diagnosis of inflammatory bowel disease in children is challenging and the final diagnosis may only be made after repeated investigations and a lapse of time.¹ In recent years white cell scanning has been advocated to demonstrate areas of inflamed bowel. Our unit has previously described the use of indium-111 tagged white cells for this purpose.^{1,2} However, this technique is associated with a high radiation burden. We wish to limit both radiation dosage and interventional procedures to the minimum consistent with adequate management. The advent of technetium-99m hexamethyl-propyleneamine oxime (Tc-HMPAO) allows superior imaging with a reduced radiation burden, using a more easily available isotope and a simple labelling technique. This investigation has been described in both adults^{3–5} and children.⁶ We present a series of children investigated prospectively using the Tc-HMPAO white cell scan (Tc-WCS), and investigate its usefulness by comparing it with barium follow through examination (Ba-FT)

where available, colonoscopic findings, and histological results from multiple colonoscopic biopsies.

Patients and methods

PATIENTS

During the period 1990 to 1993, 39 children (20 male and 19 female) were investigated prospectively for possible inflammatory bowel disease. The median age was 12.1 years (range 3.9–15.1 years). All patients had a Tc-WCS and colonoscopy with endoscopic biopsy performed, as well as an estimation of the erythrocyte sedimentation rate. Where appropriate Ba-FT examination was performed unless a previous Ba-FT had been undertaken within the preceding year. Only examinations performed within a maximum time span of 30 days were included (median three days inclusive, minimum two days, maximum 29).

METHODS

In vitro labelling of granulocytes with Tc-HMPAO was performed using a standard commercial preparation (Ceretek, Amersham International plc) by a method similar to that described by Schümichen and Schölmerich⁷; 200 MBq of isotope, scaled to the body surface area, was used. Anterior and posterior abdominal images were obtained at 20 minutes, one hour, and three hours on an Elscint LFOV gamma camera with a high resolution collimator linked to a dedicated Elscint computer. The scans were judged to be abnormal if activity was seen in the gut on the early images. Activity within the gut appearing only after three hours was taken to be normal. Quality assurance was assessed from the biodistribution in every case. No technically unsatisfactory scans occurred.

Ba-FT was performed using a low density barium (Micropaque 70% w/v), after a barium meal. A series of supine abdominal radiographs were taken, timing dependent upon the rate of transit through the bowel, with fluoroscopy and 100 mm camera images of the terminal ileum and other areas of interest as required.

Colonoscopy was performed using an Olympus PCF-20 colonoscope under intravenous sedation using pethidine (1 mg/kg) and either diazepam (0.3 mg/kg) or midazolam (0.1 mg/kg). In one patient an ileoscopy was performed via the stoma, after previous total colectomy. The proportion of the colon seen at endoscopy was recorded. Histological biopsy specimens were taken in all 39 patients, colonic and rectal in 38 (excluding the patient

Great Ormond Street
Hospital for Children
NHS Trust, London
J C Jobling
Y Yousef
I Gordon

Institute of Child
Health, London
K J Lindley
P J Milla

Correspondence to:
Dr I Gordon, Department of
Radiology, Great Ormond
Street Hospital for Children
NHS Trust, Great Ormond
Street, London WC1N 3JH.

Accepted 30 August 1995

with the previous ileostomy), and the terminal ileum in 12. Several specimens were taken from any given area and the site recorded; they were assessed by an experienced paediatric histopathologist.

The erythrocyte sedimentation rate was measured using standard laboratory techniques by our haematology department. A figure in excess of 20 mm/hour was considered to be abnormal.

ANALYSIS

The report of each examination was classified as positive or negative for inflammatory bowel disease, and the site of any positive findings was recorded; all information was then tabulated (see table 1). All cases in which results of imaging were discordant with other findings were reviewed by two of the authors (IG and JCJ). As a result of this review, six results were changed, three Tc-WCSs from negative to positive (Nos 1, 11, and 16, table 1), one from positive to negative (No 12, table 1), and two Ba-FT results from positive to negative (Nos 9 and 10). In one case (No 6, table 1) spot films from the Ba-FT were not available for review.

The histological results were taken as the ‘gold standard’ and formed the reference method against which the results of colonoscopy, Tc-WCS, and Ba-FT were assessed. Histology results were reviewed soon after the examination at a routine joint gastroenterological/pathological meeting without knowledge of the Tc-WCS or Ba-FT findings. Definitive diagnoses of Crohn’s disease or

ulcerative colitis were made only in the presence of non-caseating granulomata for the former, or severe crypt distortion and goblet cell depletion with diffuse mucosal inflammation in the latter.

Results

The results of the Tc-WCSs, colonoscopy, and histology were available in all 39 cases, as per the protocol. Ba-FTs were performed within 30 days in 31 cases. Of these, one examination was judged to have failed because of the patient’s refusal to drink an adequate quantity of barium (No 13, table 1). Histological biopsy specimens were positive for inflammatory bowel disease in 31 cases (table 1).

Of the 39 cases, all investigations (excluding erythrocyte sedimentation rate) showed positive findings of inflammatory bowel disease in 16 cases (41%) and negative findings in five cases (13%). In the remaining 18 cases (46%) there was at least one disagreement between imaging modalities and the histological results. Of the 18 cases where there was discordance of the imaging modalities, three showed negative histology. Of these, one case (No 6) was interpreted as showing positive findings of inflammatory bowel disease on Ba-FT, with a negative Tc-WCS, and an erythrocyte sedimentation rate of 15 mm/hour; endoscopy and histology showed lymphoid hyperplasia of the terminal ileum. In the second case (No 7) there was a positive Tc-WCS and a positive Ba-FT (figs 1 and 2), with the area of abnormality localised to the proximal ileum in both cases. The erythrocyte sedimentation rate was raised at 55 mm/hour. Colonoscopy was normal up to and including the terminal ileum. In the last case (No 8) there was a positive endoscopic report and the Tc-WCS was positive, with no Ba-FT performed and a raised erythrocyte sedimentation rate of 22 mm/hour. Previous endoscopy, Ba-FT, and endoscopic biopsy had demonstrated Crohn’s disease 12 months before. Cases 7 and 8 have therefore been considered as histologically negative but on overall clinical evaluation as suffering from Crohn’s disease.

In four cases, colonoscopy was normal but the histological biopsy specimens were positive. Case 9 had negative results on all three imaging techniques. Cases 10 and 11 had positive Tc-WCSs, both with negative Ba-FTs. The last, case 12, had a negative endoscopy and Tc-WCS, with no Ba-FT performed. In one case (No 13) both the Tc-WCS and Ba-FT were negative, with positive endoscopy and histological biopsy. In 10 cases (Nos 14–23) with histologically proved disease there was a negative Ba-FT, with the Tc-WCS and endoscopy being positive. One of these (No 14) was a technical failure as described above. Eight cases (21%) showed negative findings on histology, one female and seven males, average age 11.1 years. They include cases 6–8 as discussed above. Case 4, who had had the previous colectomy and ileostomy, is included in this group.

In eight patients (21%) a diagnosis of

Table 1 Summary of patient details and results of investigations (N=negative, P=positive, ND=not done)

Case No	Sex	Age (years)	Pathology	ESR* (mm/hour)	Histology	Endoscopy	Tc-WCS	Ba-FT
1	M	9	Negative	10	N	N	N	N
2	M	13	Negative	39	N	N	N	N
3	M	11	Negative	12	N	N	N	N
4	F	12	Negative†	3	N	N	N	N
5	M	10	Negative	6	N	N	N	N
6	M	7	(Lymphoid hyperplasia)	15	N	N	N	P
7	M	13	Crohn’s disease	55	N	N	P	P
8	M	14	Crohn’s disease	22	N	P	P	ND
9	F	3	Non-specific colitis	30	P	N	N	N
10	M	14	Crohn’s disease	15	P	N	P	N
11	M	11	Non-specific colitis	16	P	N	P	N
12	F	7	Non-specific colitis	16	P	N	N	ND
13	M	9	Non-specific colitis	52	P	P	N	N
14	M	9	Non-specific colitis	37	P	P	P	F
15	M	14	Non-specific colitis	4	P	P	P	N
16	F	13	Crohn’s disease	40	P	P	P	N
17	F	4	Non-specific colitis	40	P	P	P	N
18	M	11	Non-specific colitis	36	P	P	P	N
19	F	13	Eosinophilic colitis	45	P	P	P	N
20	F	15	Ulcerative colitis	30	P	P	P	N
21	F	9	Non-specific colitis	10	P	P	P	N
22	F	12	Ulcerative colitis	17	P	P	P	N
23	F	10	Ulcerative colitis	17	P	P	P	N
24	M	14	Ulcerative colitis	86	P	P	P	P
25	F	11	Crohn’s disease	50	P	P	P	P
26	F	5	Non-specific colitis	30	P	P	P	P
27	F	14	Crohn’s disease	46	P	P	P	P
28	M	13	Non-specific colitis	1	P	P	P	P
29	F	13	Non-specific ileal ulceration	12	P	P	P	P
30	M	14	Ulcerative colitis	17	P	P	P	P
31	M	14	Non-specific colitis	35	P	P	P	P
32	M	14	Eosinophilic colitis	55	P	P	P	P
33	F	12	Non-specific colitis	86	P	P	P	P
34	F	6	Ulcerative colitis	35	P	P	P	ND
35	F	14	Ulcerative colitis	33	P	P	P	ND
36	M	10	Postamoebic colitis	43	P	P	P	ND
37	F	13	Non-specific colitis	35	P	P	P	ND
38	M	13	Crohn’s disease	54	P	P	P	ND
39	F	7	Ulcerative colitis	75	P	P	P	ND

*ESR=erythrocyte sedimentation rate. †Post-total colectomy and ileostomy.

Figure 1 Case No 7: the Tc-WCS demonstrates abnormal increased activity in the left iliac fossa/flank at 25 minutes (left) with further accumulation at 90 minutes (right), consistent with active disease.

ulcerative colitis was made, six female and two male, average age 11.5 years. In five patients (13%) Crohn's disease was demonstrated, two female and three male, average age 13.0 years. Non-specific colitis was seen in 14 patients (36%), seven female and seven male, average age 9.6 years. Other diagnoses included two cases of eosinophilic colitis, one of post-amoebic colitis, and one of non-specific ileal ulceration.

Tc-WCSs were positive in 28 of the 31 histologically proved cases (figs 3 and 4) and negative in six of the eight histologically negative cases. In all cases a complete examination was successfully performed. Using histology as the reference technique, this gives a sensitivity of 90% and specificity of 75% (see table 2). If the clinical diagnosis of Crohn's disease in cases 7 and 8 is taken into account, the sensitivity becomes 90% and specificity 100%.

Figure 2 Case No 7: the Ba-FT shows abnormal fold pattern and thickening of the wall in the small bowel, corresponding to the areas of increased activity on the Tc-WCS. In spite of negative colonoscopy and histological findings, a clinical diagnosis of Crohn's disease was made.

Ba-FT examinations were performed in 31 cases, being positive in 10 of 24 histologically proved cases (sensitivity 42%) and negative in five of seven histologically negative cases (specificity 71%). Using the clinical criteria, as above, the sensitivity would be 44% and specificity 83%.

Colonoscopy was positive in 27 out of 31 histologically proved cases (sensitivity 87%) and negative in seven of eight negative cases (specificity 88%). Using clinical rather than histological criteria gives a sensitivity of 85% and specificity 100%. Colonoscopy was performed as far as the splenic flexure in all cases (except the one postcolectomy patient). The caecum was seen in 20 of these 38 cases (53%) and the terminal ileum in 12 (32%).

Discussion

In inflammatory bowel disease, particularly in Crohn's disease, symptoms and signs may be subtle and lead to considerable delay in the establishment of a diagnosis.¹ In the absence of any known aetiological agents, the histologist remains the final arbiter in the classification of inflammatory bowel disease, but imaging is of considerable importance in diagnosis and patient management.

To establish the diagnosis of inflammatory bowel disease in children it is important to use the least invasive techniques possible and the minimum radiation burden compatible with a high sensitivity and specificity. The present study was undertaken prospectively to evaluate the roles of the Tc-WCS, Ba-FT, and colonoscopy in the diagnostic process. The histology of the large bowel and ileum were taken as the reference standard for determining sensitivity and specificity. In 17 of the 31 cases in which histological changes of chronic inflammation were seen, the specific cause of the inflammatory bowel disease was ascertained. In the other 14 cases, non-specific changes were noted. Chong *et al* have compared the endoscopic biopsy findings and the histological results from surgical resections with clinical, radiological, and endoscopic findings.^{8,9} They showed that definitive diagnostic features of ulcerative colitis or Crohn's disease could be identified in only about a third of colonoscopic biopsies where a final diagnosis was made. They also identified a group in whom a diagnosis of non-specific colitis was felt applicable, and suggest that this represents a midpoint in a spectrum of inflammatory bowel disease, ranging from ulcerative colitis to Crohn's disease. In our series, we have used the diagnosis of non-specific colitis where no definite diagnostic criteria were demonstrated at histology. We recognise that while the use of colonoscopic biopsy histology as a reference standard is appropriate for children where the colon is involved in the disease, those children with disease localised to the small bowel may be deemed negative for disease, particularly where the terminal ileum has not been biopsied, yet in fact suffer from inflammatory bowel disease. Halligan *et al* have suggested that children with Crohn's disease have

Figure 3 Case No 25: an 11 year old girl with a six week history of diarrhoea. The 20 minute anterior view shows increased activity in the right iliac fossa (left), with further accumulation in this area on the one hour view (right). Colonoscopy demonstrated snail track ulceration, oedema, and inflammation of the ascending colon. Biopsy confirmed a diagnosis of localised colitis of non-specific origin.

significantly more duodenal/jejunal disease and less terminal ileal disease than in adults, and that the terminal ileum is more likely to be normal in children with small bowel disease than in adults, thus increasing the likelihood of negative ileal biopsy specimens in Crohn's disease.¹⁰

The use of radiolabelled leucocytes in the investigation of inflammatory bowel disease was first described in adults by Segal *et al*¹¹ in 1981 using indium-111 and by Schümichen and Schölmerich⁷ in 1986 using Tc-HMPAO. We have previously found indium-111 labelled white cell scans to be useful in the diagnosis of inflammatory bowel disease in childhood, but at the cost of a large radiation dose.² Tc-HMPAO gives superior images to indium, with a more suitable gamma energy and decreased radiation burden, with no beta particle emissions. The isotope is readily available in most departments. Its use in children has been

Figure 4 Case No 22: a 12 year old girl with biopsy proved ulcerative colitis. The 20 (left) and 90 minute (right) posterior views show abnormal activity above the bladder. The activity was less well seen on the anterior views suggesting distal large bowel, rather than pelvic small bowel, involvement.

Table 2 Comparison of techniques using biopsy histology as a 'gold standard'

Histology	Positive	Negative	Sensitivity	Specificity
Tc-WCS				
Positive	28	3	28/31=90%	
Negative	2	6		6/8=75%
Ba-FT				
Positive	10	14	10/24=42%	
Negative	2	5		5/7=71%
Endoscopy				
Positive	27	4	27/31=87%	
Negative	1	7		7/8=88%
Erythrocyte sedimentation rate >20 mm/hour				
Positive	21	10	21/31=68%	
Negative	3	5		5/8=63%

previously described^{6 12} but without comparison with other techniques and without strict histological correlation. We have not attempted to grade disease activity as they have but we have also used a lower dose than in those two studies, which were based on a 740 MBq adult equivalent. Our results show a high sensitivity (90%) for this relatively non-invasive technique and a specificity of at least 75% and probably approaching 100% if one uses the final clinical diagnosis as the reference method.

One of the disadvantages with Tc-WCSs is the difficulty of localising abnormal activity which may be in either the large or small bowel. Three sets of images over a three hour period does go some way to help, but accurate differentiation was not possible in many cases. We have found the use of posterior imaging to be of help in differentiating areas of increased activity in the distal colon and rectum from intrapelvic small bowel (fig 4).

A review of the results of the Ba-FT studies performed in this series of patients shows an expected preponderance of abnormalities seen in the small bowel and terminal ileum, the bulk of these cases being Crohn's disease or the non-specific group. Abnormalities in Crohn's disease were seen exclusively in the small bowel and in ulcerative colitis cases, exclusively in the large bowel. Lipson *et al* have compared the value of Ba-FT with ileoscopy with biopsy in children with Crohn's disease and found it to be highly sensitive.¹³ In our series three out of four cases examined where Crohn's disease was identified on biopsy showed abnormalities on the Ba-FT. Also noted was the diagnostic confusion seen where lymphoid hyperplasia was present. As our diagnostic criteria are somewhat different, leaving a large group with non-specific inflammatory bowel disease, it is likely that the sensitivity for Crohn's disease is similar. The Ba-FT examination is an exacting examination, and it is vital that frequent fluoroscopy and compression views are obtained.¹⁴ This makes the examination operator dependent. In the general investigation of inflammatory bowel disease the sensitivity and specificity are as expected lower than for Crohn's disease alone (42% and 71% respectively). Situations can also arise where despite the best efforts of experienced staff, patient cooperation cannot be assured, as in case number 14. The importance of a large volume of barium taken over a short period of time in optimising results has been

stressed frequently.¹⁵ This can prove difficult to accomplish particularly in younger children, and may occasion the use of intubation techniques. Together these factors result in a degree of patient stress and a considerable radiation burden. Some have felt that the rate of complicated Crohn's disease, in which the anatomical information available at follow through is of great value in the planning of operative intervention, is lower in children.¹⁰

Our rate of terminal ileal visualisation at endoscopy is lower than reported by some centres,¹² but the examination was terminated if the clinical information required had been obtained. The four cases of negative endoscopic findings where positive histological biopsy specimens were obtained (13%) serve once again to demonstrate the value of multiple biopsies in all patients, irrespective of endoscopic appearances.

CONCLUSION

For a child with suspected inflammatory bowel disease, colonoscopy with biopsy remains the investigation of choice for establishing the diagnosis. A Tc-WCS offers a non-invasive screening technique with a low radiation burden and a high sensitivity and specificity. The role of the Ba-FT requires re-evaluation. This study suggests that in the initial work-up for suspected inflammatory bowel disease there is no role for the Ba-FT. In those cases where a negative colonoscopy but positive Tc-WCS raise the possibility of Crohn's disease localised to the small bowel, the Ba-FT may be useful to define the presence of anatomically abnormal bowel. Certainly a follow through examination is indicated in children with established disease where surgery is being contemplated for a

complication of inflammatory bowel disease. However, in a child with an established diagnosis of inflammatory bowel disease in whom the activity of the inflammatory bowel disease is being questioned, we feel that the combination of a Tc-WCS and erythrocyte sedimentation rate is adequate in the absence of surgical complications.

- 1 Mosely JE, Marshak RH, Wolf BS. Regional enteritis in children. *AYR* 1960; 84: 532-9.
- 2 Gordon I, Vivian G. Radiolabelled leucocytes: a new diagnostic tool in occult infection/inflammation. *Arch Dis Child* 1984; 59: 62-6.
- 3 Reynolds JH, Graham D, Smith FW. Imaging inflammation with 99Tcm HMPAO labelled leucocytes. *Clin Radiol* 1990; 42: 195-8.
- 4 Gibson P, Lichtenstein M, Salehi N, Hebbard G, Andrews J. Value of a positive technetium-99m leucocyte scan in predicting intestinal inflammation. *Gut* 1991; 32: 1502-7.
- 5 Kennan N, Hayward M. Tc-HMPAO-labelled white cell scintigraphy in Crohn's disease of the small bowel. *Clin Radiol* 1992; 45: 331-4.
- 6 Bhargava SA, Orenstein SR, Charron M. Technetium-99m hexamethyl-propyleneamine-labeled leukocyte scintigraphy in inflammatory bowel disease in children. *J Pediatr* 1994; 125: 213-7.
- 7 Scholmerich J, Schmidt E, Schwimichen C. Scintigraphic assessment of bowel involvement and disease activity in Crohn's disease. *Gastroenterology* 1988; 95: 1287-93.
- 8 Chong SKF, Bartram CI, Campbell CA. Chronic inflammatory bowel disease in childhood. *BMJ* 1982; 284: 101.
- 9 Chong SKF, Blackshaw AJ, Boyle S, Williams CB, Walker-Smith JA. Histological diagnosis of chronic inflammatory bowel disease in childhood. *Gut* 1985; 26: 55-9.
- 10 Halligan S, Nicholls S, Bartram CI, Walker-Smith JA. The distribution of small bowel Crohn's disease in children compared to adults. *Clin Radiol* 1994; 49: 314-6.
- 11 Segal AW, Ensel J, Munro JM, Sarner M. Indium-111 tagged leucocytes in the diagnosis of inflammatory bowel disease. *Lancet* 1981; ii: 230-2.
- 12 Charron M, Orenstein SR, Bhargava SA. Detection of inflammatory bowel disease in paediatric patients with technetium-99m-HMPAO-labeled leukocytes. *J Nucl Med* 1994; 35: 451-5.
- 13 Lipson A, Bartram CI, Williams CB, Slavin G, Walker-Smith J. Barium studies and ileoscopy compared in children with suspected Crohn's disease. *Clin Radiol* 1990; 41: 5-8.
- 14 Maglinte DDT, Burney BT, Miller RE. Lesions missed on small bowel follow-through: analysis and recommendations. *Radiology* 1982; 144: 737-9.
- 15 Marshak RH, Miller RE. Enteroclysis [Letter]. *Gastrointestinal Radiology* 1980; 5: 187.