Detection of Inflammatory Bowel Disease in Pediatric Patients with Technetium-99m-HMPAO-Labeled Leukocytes

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Technetium-99m-HMPAO-labeled leukocyte imaging is now an accepted technique in the assessment of adult patients with inflammatory bowel disease (IBD), but its role in pediatric patients has not been studied. **Methods:** We evaluated the efficacy of ^{99m}Tc-HMPAO-labeled leukocyte imaging in 21 children. We studied 16 children with active IBD (4 ulcerative colitis, 10 Crohn's disease, 1 indeterminate colitis, 1 C-difficile) and 5 controls. **Results:** The sensitivity and specificity for active bowel inflammation were excellent. The intensity of uptake noted in most patients rendered image interpretation easy and straightforward. The inclusion of a tail on detector (TOD) view and anterior standing view of the abdomen is important. All patients with ulcerative colitis showed rectosigmoid disease and no small bowel activity, whereas, all patients with Crohn's disease showed discontinuous uptake and often small bowel activity. It was therefore possible to differentiate ulcerative colitis from Crohn's disease on the basis of location and distribution. **Conclusion:** The ^{99m}Tc-HMPAO-labeled leukocyte scan is an excellent technique for the detection, localization and characterization of IBD in children.

Key Words: pediatric; inflammatory bowel disease; ^{99m}Tc-HMPAO leukocytes

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Technetium-99m-hexamethylpropylemeamine oxime (HMPAO) has recently been used to radiolabel leukocytes in vitro, and promising results of its clinical use in the identification of inflammatory lesions in adults have been published (*1,2*). The ^{99m}Tc-HMPAO label has many theoretical advantages over ^{111}In-oxine labeled WBC, including better image quality, shorter acquisition time, smaller radiation dose and lower cost (*3,4*).

Inflammatory bowel diseases (IBD) include, in addition to infectious enterocolitides, two chronic idiopathic illnesses: ulcerative colitis and Crohn's disease. In 85% of patients, the two diseases may be distinguished from clinical, radiologic, endoscopic and histologic features; the remaining 15% are designated as having "indeterminate colitis." These important causes of chronic illness in children and adults frequently begin in late childhood or adolescence (*5*). They are characterized by unpredictable exacerbations and remissions and variable response to therapy. Distinguishing the two diseases, monitoring their progression and tailoring their therapy are major challenges incompletely met by currently available diagnostic tools.

The aim of this study was to evaluate the applicability of ^{99m}Tc-HMPAO-labeled leukocyte imaging in pediatric IBD and to characterize technical aspects important in the evaluation of these diseases.

MATERIALS AND METHODS

Patients

We studied 21 children: 5 control patients without IBD (1.5–16 yr) and 16 patients with IBD (3–20 yr). The diagnoses for controls were osteomyelitis (3), fever of unknown origin (1) and irritable bowel syndrome (1). The diagnoses for IBD patients were ulcerative colitis (4); Crohn's disease (10); indeterminate colitis (1); and infectious enterocolitis (1, C. difficile). All patients were symptomatic with abdominal pain or diarrhea, and most had an abnormal ESR.

Imaging

Twenty to 45 ml of venous blood was withdrawn into a 60-ml syringe containing 7 ml of ACD solution. Five milliliters of 6% hetastarch® was added and mixed. The syringe was inverted and allowed to settle for 40 to 60 min. The leukocyte-rich plasma (LRP) was collected and centrifuged at 300 g for 5 min. The HMPAO vial was reconstituted with 1110 MBq of ^{99m}Tc (3 ml) and radiochemical purity was tested. Technetium-99m-HMPAO (925 MBq) was added to the leukocyte button and mixed gently. This mixture was incubated for 15 min. Five milliliters of platelet-rich plasma (PRP) were added and centrifuged for 5 min. The ^{99m}Tc-leukocyte button was reconstituted in 5 ml PRP and assayed in a dose calibrator. The adult patient dose, 740 MBq, was adjusted by weight for children. The blood was then reinjected intravenously. At 0.5–1 hr, 2–3 hr and 4 hr postinjection, imaging was performed with a LFOV gamma camera (Siemens Orbiter, Des Plaine, IL) fitted with a low-energy, high-resolution collimator. Anterior, posterior and lateral 5-min images of the abdomen and pelvis were recorded in analog and digital form. Tail on

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TABLE 1
Distribution and Intensity of Uptake

Name	Diagnosis	Rectosigmoid	Descending	Transverse	Ascending	Small bowel	Total
J.D.	Ulcerative colitis	3	1	1	1	0	3
L.A.	Ulcerative colitis	3	2	1	2	0	3
N.G.	Ulcerative colitis	3	3	3	3	0	3
B.S.	Ulcerative colitis	3	1	1	2	0	3
L.A.	Crohn's disease	3	2	1	0	0	3
J.A.	Crohn's disease	0	1	1	2	3	2
L.B.	Crohn's disease	0	2	0	3	3	3
N.D.	Crohn's disease	3	1	1	3	2	3
M.E.	Crohn's disease	3	3	3	3	2	3
C.K.	Crohn's disease	0	1	0	2	0	2
T.S.	Crohn's disease	0	0	0	1	2	1
J.W.	Crohn's disease	3	3	3	3	0	3
P.J.	Crohn's disease	2	1	2	0	0	2
A.C.	Crohn's disease*	0	2	3	3	0	3
L.H.	C-diff	0	1	0	1	0	1
K.A.	Indeterminate IBD	0	1	0	1	0	1
J.G.	Normal (irritable)	0	0	0	0	0	0
W.P.	Normal (osteo)	0	0	0	0	0	0
A.V.	Normal (osteo)	0	0	0	0	0	0
A.A.	Normal (fuo)	0	0	0	0	0	0
S.P.	Normal (osteo)	0	0	0	0	0	0

*Also X-linked aggamaglobulinemia.

detector (TOD) projections were also obtained to distinguish bladder activity from rectal activity. Finally, anterior views of the abdomen with the patient standing were obtained to differentiate the liver from transverse colon.

Image Evaluation

In each of the three sets of scans (0.5–1 hr, 2–3 hr, and 4 hr) the bowel was divided into five segments (rectosigmoid, descending, transverse, ascending colon, and small bowel), resulting in 315 bowel segments for scoring (i.e., 21 patients × 3 images × 5 segments = 315). Inflammatory activity in each segment was graded semiquantitatively by comparing the uptake in the bowel with that in the iliac crest bone marrow: Grade 0 = no activity; Grade 1 = activity less than iliac crest; Grade 2 = activity similar to iliac crest; and Grade 3 = activity greater than iliac crest. Unless specifically identified as delayed images, the grades reported below refer only to those scores from the first hour. In addition to the scoring of each of the 315 bowel segments, each patient received an overall score consisting of the highest grade in any bowel segment.

Patients with continuous uptake from the anus orad, and with uptake limited to colon, were considered to have ulcerative colitis. Patients without rectosigmoid activity or discontinuous (segmental, patchy) (*5*) colonic uptake, or with small bowel uptake were considered to have Crohn's disease. All images were interpreted by one nuclear physician (MC) who was blinded to the clinical details.

RESULTS

Normal Distribution of Uptake: Controls

Normal uptake distribution during the first hour was similar to that reported in adults and is characterized by uptake in the lungs, liver, spleen, bone marrow and bladder (*6*). The kidney and renal pelvis were occasionally visualized. At 4 hr, lung activity was minimal and bone marrow uptake was more marked, whereas the activity in liver, spleen, kidneys and bladder remained unchanged. Although intestinal accumulation is reported to occur in the normal ascending colon at 4 hr (*2,3,6,7*) and rarely before, no such false-positive activity was seen in our controls. We did not find renal excretion of ^{99m}Tc-HMPAO to interfere with scan interpretation.

Localization of Uptake: Patients (Table 1)

All four patients clinically diagnosed as having ulcerative colitis had rectosigmoid involvement with maximal activity (Grade 3) in this location (Fig. 1). There were no "skip" lesions and no evidence for abnormal uptake in the small bowel in these patients. In contrast, all active Crohn's disease patient scans manifested discontinuous uptake (Fig. 2). Small bowel activity was seen in five patients. Two patients with Crohn's disease had uptake observed in the esophagus. The patients with indeterminate colitis and C. difficile enterocolitis each showed only Grade 1 uptake in the descending and ascending colon. No patient had abnormal uptake in their joints.

Two patients had incorrect initial disease classifications prior to imaging; the correct classifications were suggested by the scans and were subsequently proven surgically. The first of these was a patient referred to our center with a diagnosis of ulcerative colitis, but whose scan results documented small intestine disease indicative of Crohn's disease (Fig. 3). The other patient was initially diagnosed as having indeterminate colitis, but his Grade 3 rectosigmoid involvement and the lack of skip lesions or small intestine involvement correctly predicted the surgical diagnosis of ulcerative colitis (Fig. 1).

Degree of Uptake by Disease

The distribution of intensity of uptake by disease was as follows: the four cases of ulcerative colitis showed Grade 3 uptake; the 10 cases of Crohn's disease disclosed Grade 3 uptake in six patients, Grade 2 uptake in 3 patients and Grade 1 uptake in one patient. In the cases of indeterminate colitis and infectious colitis, only Grade 1 uptake was presented. No uptake was noted in the controls.

Patients: Temporal Pattern of Uptake

All 14 patients with very abnormal uptake (Grade 3) demonstrated the abnormality within 1 hr. There was no movement of activity with time that could suggest excretion of ^{99m}Tc in the bowel lumen. We concluded that sensitivity was not increased, but specificity could be lost when using only the 4-hr delayed image.

Technical Considerations

The standing view disclosed otherwise undetectable abnormal uptake in the transverse colon in two patients. The TOD projection disclosed otherwise nonvisualized rectal and perianal disease in most patients with such disease. The lateral views provided no additional information for any patient because of the high attenuation from the pelvic bony structures.

The sensitivity of this technique for detecting IBD was excellent. The time spent at the hospital for testing and imaging was approximately 25% shorter than that for ^{111}In-WBC imaging and is similar to that for air contrast barium enemas and small bowel series as well as sedated upper and lower endoscopies with biopsies. Acquisition time (and thus use of the nuclear medicine facilities) is approximately half of that needed for ^{111}In-WBC scans. In adults, the radiation exposure is approximately one-third less than that for an ^{111}In-WBC scan.

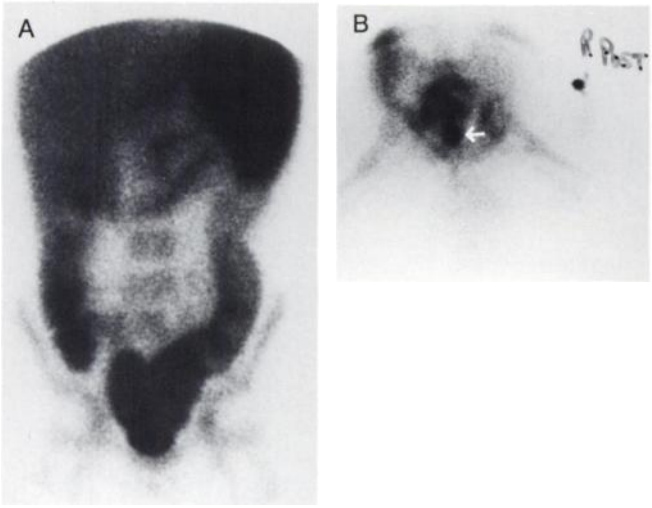

FIGURE 1. (A) Grade 3 uptake in a patient with ulcerative colitis localized in the entire large colon with no small bowel uptake. The transverse colon shows less uptake, probably because of its posterior location. (B) TOD view differentiates bladder activity (arrow) from rectal activity.

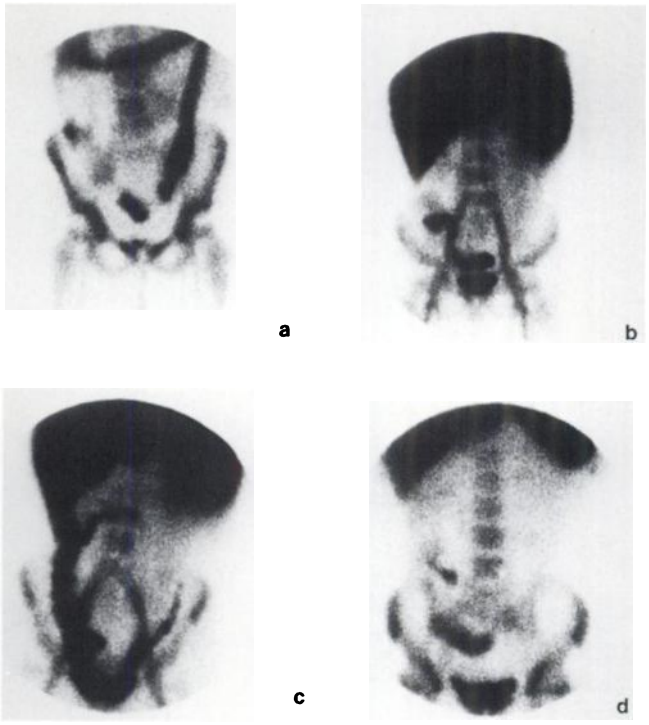

FIGURE 2. Four different Crohn's disease patients with discontinuous uptake. (A) Grade 3 uptake is noted in the descending and transverse colon, whereas the ascending colon reveals discontinuous uptake. (B) Discontinuous Grade 3 uptake in a portion of the ascending colon and terminal ileum. The lack of uptake in a continuous fashion beginning in the rectum clearly militates against ulcerative colitis. (C) Skip area in the descending-transverse colon suggests Crohn's disease. (D) Discontinuous uptake in the ascending colon and terminal ileum.

DISCUSSION

Localizing and quantifying inflammation in Crohn's disease and ulcerative colitis is crucial to determining diagnosis, prognosis and optimal therapy (both pharmacologic and surgical); especially since the small intestine has been particularly inaccessible to evaluation.

Fluoroscopic methods show only indirect evidence for inflammation (edema, fibrosis, ulceration) and entail considerable radiation exposure. Endoscopic methods require sedation, involve some risks from the instrumentation, and miss most of the small bowel. Both types of studies require uncomfortable and/or prolonged colon cleansing, significant physician time and two separate procedures for optimal evaluation of small and large bowel.

A nuclear medicine leukocyte scan has the potential for quantifying and localizing inflammation directly, while overcoming the disadvantages of fluoroscopy and endoscopy. Unfortunately, until recently only the ^{111}In-labeled leukocyte scan was available; its radiation exposure and duration of imaging, however, made it a relatively poor technique, particularly for children.

Technetium-99m-HMPAO-labeled leukocyte imaging, on the other hand, overcomes the problems of ^{111}In-WBC imaging. Technetium-99m-HMPAO-labeled leukocytes

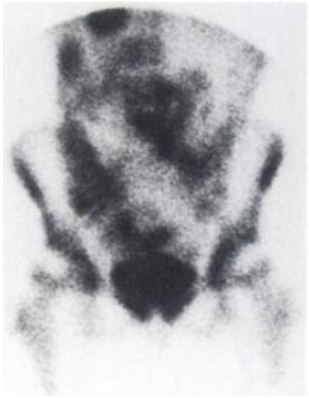

FIGURE 3. This patient, originally thought to have ulcerative colitis, had a scan that revealed small bowel uptake indicative of Crohn's disease.

have been used successfully to image a wide variety of inflammatory diseases (*9,11–18*). Intra-abdominal infections have been detected as early as 0.5 hr postinjection (*10,11*).

In ulcerative colitis, the inflammation extends in a continuous, uniform fashion proximally from the rectum (*5*). In contrast, the inflammation in Crohn's disease is discontinuous, segmental and patchy. On the basis of location and distribution of inflammation, one can usually differentiate ulcerative colitis from Crohn's disease; we verified that the patterns observed on the scans corresponded to the clinical diagnoses. All patients with ulcerative colitis showed rectosigmoid disease, continuous uptake (no skip lesion) and no small bowel activity. In contrast, patients with Crohn's disease showed discontinuous uptake (focal, skip lesion) and often small bowel activity.

In our study, the localization of uptake was simplest in patients with ulcerative colitis, in whom colonic uptake was continuous, maximal (Grade 3) and without small bowel activity. In patients with Crohn's disease, however, it can be difficult to distinguish the large bowel from small bowel due to the discontinuous distribution of disease (Fig. 2D).

Our single cases of indeterminate colitis and C. difficile enterocolitis suggest that these diseases may manifest less bowel uptake than Crohn's disease or ulcerative colitis, but our patient population is too small to derive firm conclusions; further studies are needed.

We unexpectedly observed esophageal uptake in two patients with Crohn's disease; we do not know whether this represents esophageal distribution of the disease itself. Further study is needed to confirm this association. Our patients showed no uptake in their joints, but none had joint symptoms. It will be interesting to evaluate joint uptake in patients with articular manifestations of IBD in a future study.

The intensity of uptake observed in our patients was striking and rendered straightforward images that were easy to interpret. This consistently high degree of uptake may be due in part to reduced attenuation of the radionuclide in these smaller patients. Although selection bias may have led us to study only patients with relatively severe disease, a similar bias likely occurred in the adult studies.

The temporal pattern of uptake we observed confirmed the suggestion by others (*2,3,8,10*) that little additional sensitivity is achieved, and specificity might be lost (excretion in ascending colon) on images acquired beyond 3 or 4 hr after injection of the radionuclide. Exceptions might occur when the initial image shows questionable uptake. The lack of temporal change in uptake distribution militated excretion of ^{99m}Tc in the bowel lumen.

The diagnostic benefits of the two technical modifications we used were clearly demonstrated. The transverse colon was revealed separate from the liver by the standing projection. In contrast to results reported by others (*2*), perianal and rectal disease were easily delineated by the TOD projection, which separated these areas from the bladder and can overlap them on the anterior projection. In contrast, the lateral projection provided no additional information and we do not advocate its use. We now routinely image the abdomen in the anterior and posterior supine, pelvic outlet and standing projections between 30 min and 1 hr.

In conclusion, the ^{99m}Tc-HMPAO-labeled leukocyte scan is an excellent technique for the detection, localization and characterization of IBD in children. Compared to other methods, such as fluoroscopy, endoscopy and ^{111}In-WBC scanning, the ^{99m}Tc-HMPAO-labeled leukocyte scan requires no bowel preparation or discomfort, and is relatively noninvasive, relatively economical compared to endoscopy and has excellent diagnostic sensitivity. Although its exact role in the diagnosis and management of pediatric inflammatory bowel diseases requires further definition, our results suggest that this role may be substantial.

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