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Scintigraphy with ^{99m}Tc-HMPAO labeled leukocytes is still an accurate and convenient tool to rule out suspected inflammatory bowel disease in children

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Abstract

BACKGROUND: Abdominal pain is a common complaint in children and its differential diagnosis includes inflammatory bowel disease (IBD). The aim of the study was to assess the diagnostic accuracy of scintigraphy with ^{99m}Technetium Hexamethylpropyleneamine Oxime (^{99m}Tc-HMPAO) labeled leukocytes in children with suspected IBD.

MATERIAL AND METHODS: Eighty-five children (age 12.4 ± 4.3 years, 47% boys) with suspected IBD based on clinical presentation, laboratory and ultrasound findings underwent scintigraphy with ^{99m}Tc-HMPAO labeled leukocytes. Abdominal scintigrams were acquired 40 min and 90 min post injection, and whole body scintigrams at 180 min. Scintigraphy was evaluated by two specialists in nuclear medicine. The results were compared with the final diagnosis established by endoscopy, histology, other imaging methods, and follow-up evaluated by an expert in pediatric gastroenterology.

RESULTS: Scintigraphy results corresponded with the final diagnosis in 78 (91%) patients resulting in a sensitivity of 89% (95% CI 72 to 98%), specificity of 91% (95% CI 82 to 98%), and accuracy of 91% (95% CI 83 to 96%). The interobserver agreement was 0.82 (95% CI 0.75 to 0.88) and the radiation dose estimate was 4.2 ± 1.5 mSv. In 28 children (25 positives and 3 negatives on scintigraphy), the diagnosis of IBD was established by endoscopy, histology, MR enterography, or fluoroscopy. Five positive findings on scintigraphy were not confirmed by other methods or during follow-up.

CONCLUSION: Scintigraphy with ^{99m}Tc-HMPAO labeled leukocytes in children with suspected IBD has high accuracy and offers a non-invasive option for detecting the presence of gastrointestinal inflammation. Scintigraphy is a powerful non-invasive decision-making tool in the management of suspected IBD that may spare a greater proportion of children of more invasive and demanding examinations.

KEY words: scintigraphy, ^{99m}Tc-HMPAO, leukocyte, inflammatory bowel disease

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Introduction

Abdominal pain is one of the most common complaints in children [1]. In up to 95% of these children, no underlying cause can be detected, but is essential to identify the remaining 5% with organic pain [2–4]. Although the differential diagnosis is very broad and varies with age, the possibility of inflammatory bowel disease (IBD) should be considered. The incident rate of IBD is increasing and its first clinical presentation can be traced to an even younger age [5]. IBD etiology remains obscure. A coincidence of genetic predispositions, environmental factors and changes in the gut microbiome is suspected [6]. IBD encompasses the Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU) [7]. CD is the most frequent type of IBD in children with a prevalence of 58 per 100 000 children [8, 9]. CD can affect any part of the gastrointestinal (GI) tract from the mouth to anus, most commonly ileum and colon.

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The diagnosis of IBD is based on clinical presentation, laboratory tests, endoscopic findings, histology, and imaging [7, 10, 11]. Abdominal ultrasound is the first-line imaging modality, but GI scintigraphy can be useful in the early phase of investigation as well [12]. GI scintigraphy with ^{99m}Technetium Hexamethylpropyleneamine Oxime (^{99m}Tc-HMPAO) labeled leukocytes evaluates the location and the severity of the suspected inflammation and has been used in this indication for over 20 years. It has a high sensitivity for detecting IBD with a high negative predictive value but the awareness about its usefulness is waning [11, 13, 14]. Finding of inflammatory activity in the bowel on scintigraphy would warrant more invasive examinations as colonoscopy. Although MR enterography (MRE) is considered the imaging modality of choice (after first-line ultrasound) due to excellent visualization of the small bowel, satisfactory depiction of large bowel, and the absence of radiation burden, it requires good cooperation of the child, who has to drink a considerable amount of contrast material and hold breath when asked. Motion artifacts and poor bowel distension may render MR enterography non-diagnostic in some cases [15].

The goal of this study was to evaluate the diagnostic performance of scintigraphy with ^{99m}Tc-HMPAO labeled leukocytes in the detection of IBD in children and to revisit the role of scintigraphy in the diagnostic workflow of children with suspected IBD.

Patients and methods

This retrospective study was performed in accordance with the Declaration of Helsinki, it was approved by the local Ethics Committee, and informed consent was waived.

Altogether 85 consecutive children between 4 and 18 years (12.4 ± 4.3 years, 47% boys) with abdominal complaints, who were examined by ^{99m}Tc-HMPAO labeled leukocytes GIT scintigraphy between January 2010 and March 2018, were enrolled in the study. The examination was requested after detailed physical and laboratory examinations, and abdominal ultrasound for diagnostic uncertainty that could suggest IBD.

The children were examined fasting. A total of 0.5–1 ml of blood per kg of body weight (average weight 44 ± 17 kg) was sampled into sterile syringes with aliquot amounts of anticoagulant citrate dextrose solution and 6% hydroxyethyl starch. The leukocyte separation and their labeling was performed according to the manufacturer's manual with the following steps: 1) spontaneous sedimentation of erythrocytes, 2) supernatant centrifugation, 3) separation of leukocytes, and 4) their labeling with ^{99m}Tc-HMPAO in an amount based on the child's weight followed by 5) incubation at room temperature, 6) centrifugation for acquiring blood plasma and 7) removal of free ^{99m}Tc-HMPAO. A suspension of labeled leukocytes with an activity of 175–700 MBq was then ready to be re-injected into the systemic circulation. The administered amount of activity for children was derived from adult values and modified based on the child's body surface area as listed in tables published by the European Association of Nuclear Medicine (EANM).

Scintigraphic images were acquired at 40, 90 and 180 minutes after the administration of ^{99m}Tc-HMPAO labeled leukocytes using INFINIA gamma camera (GE Healthcare, Waukesha, WI, USA). The camera was fitted with a low-energy high-resolution parallel collimator. Early static images of the abdomen were acquired 30–40 minutes after the administration of labeled leukocytes in an anterior and posterior projection, 500000 counts per image, and a matrix of 256 × 256 pixels. Single Photon Emission Computed Tomography (SPECT) of the abdomen was performed 90 minutes after the administration of labeled leukocytes. The following acquisition parameters were used: 60 images, 30–40 seconds per image, 128 × 128 pixel matrix. Whole body images were taken 3 hours after the administration of labeled leukocytes in an anterior and posterior direction with a table movement speed of 5–10 cm per minute. Zoom was used as necessary.

The acquired images were evaluated both visually and semi-quantitatively using Cheow score [16] by an experienced physician blinded to the patients' clinical data and outcome. Based on this score, the findings could be differentiated into 3 categories based on the degree and extent of pathologic activity (Tab. 1).

IBD was suspected when uptake (at least 1A by Cheow score) was present in the early abdominal images and became more pronounced in the late images.

To assess interobserver agreement, randomly selected 42 scans were independently assessed by another nuclear medicine physician.

Radiation dose was calculated using conversion coefficients of 0.034 mSv/MBq for children up to 5 years and 0.011 mSv/MBq for older.

As the gold standard, we used the results of endoscopy with biopsy, other imaging modalities, and follow-up examinations evaluated by an experienced pediatric gastroenterologist.

The statistical analysis was performed in Medcalc v.15 (Medcalc software bvba, Ostend, Belgium). Sensitivity, specificity, and accuracy were calculated with their 95% confidence intervals (CI). Cheow score was compared by the Wilcoxon test. Interobserver agreement was expressed as kappa statistics. A p-value below 0.05 was considered significant.

Results

Scintigraphy findings corresponded with the final diagnosis in 78 (91%) of the 86 patients resulting in a sensitivity of 89% (95% CI

Table 1. Scintigraphy results and the Cheow score — early and late phase

	Patients with IBD n = 28		Patients without IBD n = 58	
Cheow score				
Scintigraphy phase	Early	Late	Early	Late
No activity	2	0	50	22
Degree of activity				
1 — Barely detectable pathologic activity in the abdominal cavity	2	0	3	13
2 — Between category 1 and 3	7	3	4	22
3 — Abnormal uptake with activity at least as high as bone marrow	17	25	1	1
Extent				
A — Single focus	2	0	1	9
B — Between category A and C	14	7	6	26
C — Diffuse inflammation	10	21	1	1
Evaluation				
IBD by scintigraphy	25		5	

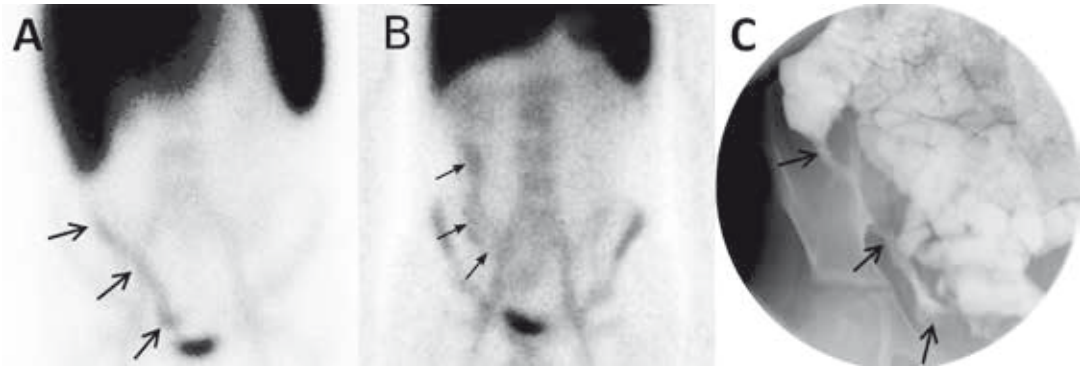

Figure 1. Crohn's disease with ileocecal involvement. An early scintigram in a 12-year-old boy with a pathologic accumulation of labeled leukocytes in the right lower abdominal quadrant corresponding with the location of the terminal ileum, caecum, and the ascending colon (Cheow score 3C) confirms the presence of Crohn's disease **(A)**. A late scintigram with even more conspicuous pathologic accumulation (Cheow score 3C) in the same location **(B)**. Small bowel follow through in the same boy shows cobblestoning and irregular luminal narrowing as typical features of Crohn's disease in the terminal ileum, caecum and the ascending colon using MR enterography **(C)**

72 to 98%), specificity of 91% (95% CI 82 to 98%), and accuracy of 91% (95% CI 83 to 96%). In 28 children (25 positives and 3 negatives on scintigraphy), the diagnosis of IBD (26 Crohn's disease, 1 ulcerative colitis, 1 indeterminate) was established by endoscopy, histology, MR enterography, or fluoroscopy (Fig. 1 and Fig. 2). From 56 children with negative scintigraphy, three were ultimately diagnosed with IBD (all Crohn's disease). Five positive scintigraphy findings were not confirmed by other methods or during follow-up.

The Cheow score was significantly higher both in the early and late phase in patients with IBD ($p < 0.0001$, Tab. 1). The interobserver agreement was 0.82 (95% CI 0.75 to 0.88) and the radiation dose estimate was 4.2 ± 1.5 mSv. In 6 patients, scintigraphy found other locations of inflammation in the joints.

Discussion

In this study, we showed that scintigraphy with ^{99m}TC-HMPAO labeled leukocytes in children with suspected IBD has high sensitivity for detecting the presence of inflammation in the gastrointestinal tract. The examination has an almost perfect interobserver agreement and exposes other foci of inflammation in the body.

Nuclear medicine has proved usefulness in detecting inflammatory activity. Labeled leukocytes scintigraphy became an integral part of diagnostic algorithms. Leukocytes, monoclonal antibodies or their fragments labeled with ^{99m}Tc or ^{111}In have been used. ^{111}In is not suitable for imaging in children due to high radiation burden, and monoclonal antibodies are not routinely used in pediatrics as well. Therefore, scintigraphy with ^{99m}TC-HMPAO labeled leukocytes became the method of choice in children [16]. HMPAO is a complex molecule with lipid affinity, capable of penetrating blood cells. Once this molecule is internalized, it becomes hydrophile and remains inside the cell [17]. HMPAO shows a high affinity to granulocytes, where it remains in 86% [18]. Due to this complex action, it is used for the detection of inflammatory activity including IBD. Scintigraphy can also be used in patients with an already established diagnosis to evaluate treatment response and the degree of the inflammatory activity [19–21].

The presence of inflammatory activity detected using scintigraphy in children with abdominal complaints warrants further investigation. These further indicated methods are usually more demanding requiring special preparation, anesthesia, or sedation. The cutting advantage of scintigraphy as a non-invasive screening test is its high sensitivity in identifying inflammation which is reported between 88% and 93% which is comparable with the results of our study [22, 23]. It is important to remember though, that this method has lower specificity ranging between 81% and 91% [22, 23]. Another drawback is that scintigraphy does not show anatomic changes in the GI tract, mainly lumen narrowing, fistula formation and prestenotic dilatations.

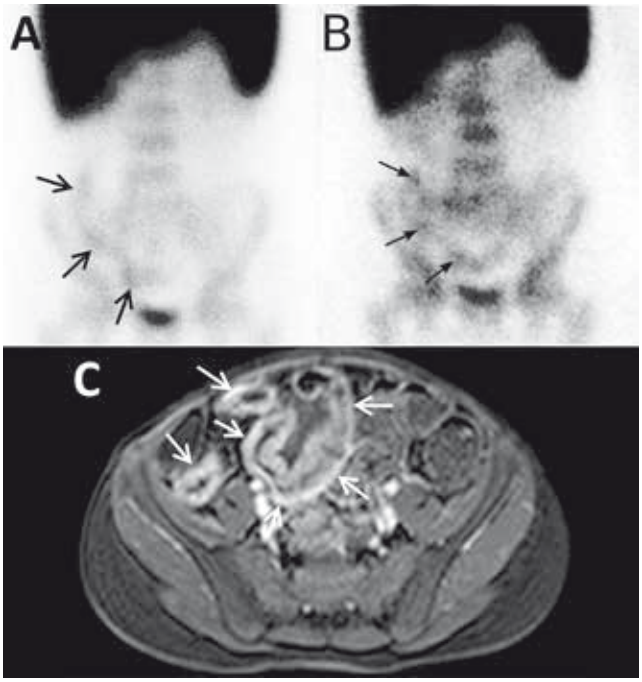

Figure 2. Crohn's disease with ileocecal involvement. An early scintigram in an 11-year-old boy with a pathologic accumulation of labeled leukocytes in the right lower abdominal quadrant corresponding with the location of the terminal ileum, caecum, and the ascending colon (Cheow score 3C) confirms the presence of Crohn's disease **(A)**. A late scintigram with even more conspicuous pathologic accumulation (Cheow score 3C) in the same location **(B)**. MR enterography shows marked thickening and mural enhancement of the ileum on a T1 (THRIVE) transversal section **(C)**

Intestinal non-specific activity is usually present early in the course of the examination due to biliary excretion of the primary lipid soluble complex or its secondary metabolites. In adults, this activity is present within the first two hours since the application of the labeled leukocytes [24]. In children, it can be visible within the first hour. This only emphasizes the importance of obtaining early images in children while this non-specific activity is not present.

During the last decade, new diagnostic methods for the detection and localization of inflammation including scintigraphy with ^{99m}Tc-DMSA (Dimercaptosuccinic Acid) [25], ^{18}F-FDG PET and PET/CT have been introduced into practice [13, 14, 26, 27]. Due to its high radiation burden, PET/CT is not regarded as the method of choice in diagnosing IBD in children and the evidence on the utility of ^{18}F-FDG PET/CT in IBD is limited [28]. More recently, a retrospective study of Catalano et al [29] investigated the role of ^{18}F-FDG PET/MRE in discriminating between inflammatory and fibrotic strictures associated with CD. Another study documented that PET/MRE is more accurate than PET/CT in assessing extraintestinal disease in patients with CD [15, 30].

In comparison with another nuclear medicine imaging examinations by the radiation burden and price, scintigraphy with ^{99m}Tc-HMPAO labeled leukocytes is the most efficient tool in the detection of IBD in children, providing information on the presence, the activity and the extent of active disease, particularly in the terminal ileum. According to our experience and in accordance with paper of Catalano et al. [14] this examination allows the evaluation of areas of bowel that cannot be explored with colonoscopy and it could represent a non-invasive procedure not only for the diagnosis but also for follow-up and therapy monitoring in children. Compared to MRE, scintigraphy can find all locations affected by inflammation, including the stomach, perianal disease, reactive arthritis, and even enterocutaneous manifestations.

For ethical reasons, only a minority of children with negative findings on scintigraphy underwent endoscopy, MRE, fluoroscopy to confirm the absence of IBD, which is the most important limitation of this study.

Conclusion

Scintigraphy with ^{99m}TC-HMPAO labeled leukocytes in children with suspected IBD has high accuracy and offers a non-invasive option for detecting the presence of gastrointestinal inflammation. It also exposes other foci of inflammation in the body. Scintigraphy is a powerful non-invasive decision-making tool in the management of suspected IBD that may spare a greater proportion of children of more invasive and demanding examinations.

Conflict of interest:

The authors declare that there is no conflict of interest regarding publication of this article.

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Author contributions:

1. Study concept and design: DC
2. Acquisition of data: all
3. Analysis and interpretation of data: all
4. Drafting of the manuscript: DC
5. Critical revision of the manuscript for important intellectual content: all
6. Statistical analysis: JT, LL
7. Administrative, technical, and material support: all
8. Study supervision: DC

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