^{99m}Tc-Human Serum Albumin Scans in Children with Protein-Losing Enteropathy

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Protein-losing enteropathy (PLE) can be diagnosed scintigraphically using ^{99m}Tc-human serum albumin (HSA) scans. **Methods:** To evaluate the usefulness of this method in detecting enteric protein loss, we retrospectively reviewed the ^{99m}Tc-HSA scans of 18 children presenting consecutively with PLE. **Results:** Enteric ^{99m}Tc-HSA uptake was noted in 12 patients (8 boys, 4 girls) with a mean age of 7.4 y. Early dynamic images showed abdominal uptake that was most likely in the small bowel in 91% of the scans. Delayed images showed abnormal accumulation that was localized in the colon in 73% and in the small bowel in 27% of the scans. A 4-mo follow-up scan obtained in 3 patients showed reduced HSA uptake after a high-protein, low-fat, medium-chain triglyceride oil-based diet and fat-soluble vitamins. Mean serum albumin, total protein, gammaglobulin, and calcium levels were significantly decreased. Ten patients (from 4 families) were diagnosed to have primary intestinal lymphangectasia. One patient had active *Salmonella* enterocolitis, and 1 had giardiosis. ^{99m}Tc-HSA was normal in the remaining 6 patients (3 boys, 3 girls) with a mean age of 3.5 y (range, 2–5 y). Mean serum albumin, total protein, gammaglobulin, and calcium levels were less decreased than those of the first group. Five of these patients had primary intestinal lymphangactesia (associated with infantile systemic hyalinosis in 1 patient). The remaining patient had normal duodenal biopsy, and the cause of protein loss remained unknown. **Conclusion:** The ^{99m}Tc-HSA scan is useful in the evaluation of children with PLE, especially those with severe hypoproteinemia and hypoalbuminemia, presumably reflecting a high rate of protein loss.

Key Words: ^{99m}Tc-human serum albumin; protein-losing enteropathy; primary intestinal lymphangectasia

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Protein-losing enteropathy (PLE) can be the result of primary intestinal lymphangectesia (PIL) or secondary intestinal lymphangectesia in association with cardiac diseases or obstructed lymphatics. Abnormal or inflamed mucosal surface secondary to intestinal inflammation/infection, immunologic, inflammatory, and vasculitic disorders can also cause enteric protein loss (*1*). This pathophysiologic condition generally results from an abnormal mucosal permeability, desquamation, inflammation, or back-pressure in the intestinal lymphatic network (*2*). The protein loss is nonselective and includes plasma proteins such as albumin, globulins, and transferrin. Radiolabeled proteins that have been used for determining enteric protein loss include ^{131}I-albumin, ^{51}Cr-albumin, and ^{67}Cu-ceruloplasmin (*1*). They are not widely used because of limitations, such as the need for stool collection over several days, the requirement that the stool is not contaminated by urine, the characteristics of the tracers, and limited availability (*1*). Recently, ^{99m}Tc-human serum albumin (HSA) has been successful in localizing the site of enteric protein loss in adults (*3–9*). However, the literature is scarce concerning pediatric patients (*10–12*).

In this study, we present our experience with ^{99m}Tc-HSA scanning in 18 children with known PLE.

MATERIALS AND METHODS

Medical records of 18 children consecutively referred with a diagnosis of PLE and who had undergone ^{99m}Tc-HSA scanning were reviewed retrospectively.

Laboratory Measurements

Serum total protein, albumin, and total calcium were determined using kit reagents according to directions provided by the manufacturer (BM/Hitachi 917 System Pack; Boehringer-Mannheim Biochemicals, Mannheim, Germany). Pediatric normal reference ranges were 50–60 g/L for protein, 30–40 g/L for albumin, and 2.1–2.6 mmol/L for calcium. Corrected calcium was calculated according to the albumin level, using the following equation: calcium level + [40-albumin] × 0.02 = corrected calcium.

Serum gammaglobulin concentration was determined using immunoglobulin-specific antisera (rabbit) according to instructions provided by the manufacturer (Roche Diagnostics, Basel, Switzerland). Pediatric reference ranges were 3.5–12.4 g/L.

Absolute lymphocyte count was calculated from the differential blood count determined in a Coulter counter (CSTK-S). Lymphocytopenia was also confirmed manually. All laboratory measurements were performed in the Clinical Biochemistry section of the Department of Pathology and Laboratory Medicine at the King Faisal Specialist Hospital and Research Centre.

Statistical Analysis

Statistical analysis of the laboratory results was performed using the Wilcoxon method to calculate the P value (considered significant at <0.05).

^{99m}Tc-HSA Scans

Anterior abdominal scintigraphy was performed in all patients after the intravenous injection of freshly prepared ^{99m}Tc-HSA.

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The administered age-adjusted doses using a modified Young's or Webster's rule (*13*) were 185–503 MBq (5–14 mCi) based on an adult dose of 740 MBq (20 mCi). Dynamic images were acquired every minute for 1 h, using an all-purpose collimator and a large-field-of-view γ-camera. Additional delayed images were obtained at 2–6 h in most patients and 24 h in a few patients. The possibility of in vivo breakdown of the tracer and false-positive localization with free pertechnetate was excluded by the absence of stomach visualization in all studies. All scans were retrospectively reviewed by 2 nuclear medicine physicians and evaluated as to the presence and location of intestinal activity. The intensity of the uptake was visually graded according to the liver activity, as follows: 3 = marked uptake (equal to liver); 2 = moderate uptake (less than liver); 1 = mild uptake. Consensus readings were used for the final interpretation.

RESULTS

Twelve children (8 boys, 4 girls; age range, 1–14 y; mean ± SD, 7.4 ± 4 y) were found to have abnormal HSA accumulation in the gut. The clinical features, biochemical data, histological diagnosis, and scintigraphic findings of the 12 children who showed enteric uptake on the ^{99m}Tc-HSA scans are summarized in Table 1.

Dynamic images showed abdominal uptake most likely in the small bowel (Figs. 1A and 2A) in 91% (10/11) of the scans performed (early dynamic images were not acquired in 1 child with positive delayed images). Delayed images showed abnormal accumulation that was localized in the colon (Fig. 2B) in 73% (8/11) and in the small bowel (Fig. 1B) in 27% (3/11) of the scans performed (delayed images were not acquired in 1 child with positive early images). The mean total protein was 31.7 g/L (range, 25–40 g/L), mean serum albumin level was 17 g/L (range, 14–20 g/L), and mean gammaglobulin was 2.8 g/L (range, 1.5–4.4 g/L). The mean corrected calcium level was 2 mmol/L (range, 1.5–2.5 mmol/L), and mean absolute lymphocyte count was 1657 (range, 330–4000). The clinical manifestations among these 12 children included generalized edema in 92%, growth failure in 67%, diarrhea in 50%, recurrent infection (chest and skin) in 42%, and seizures in 17%.

Primary intestinal lymphangectasia (PIL) was the underlying clinical diagnosis in 9 children from 4 families (2 or 3 children affected from each family) and in 1 sporadic case. First-degree consanguinity was documented in 80% (4/5) of parents. Four patients were confirmed histologically, and the diagnosis was based on the clinical presentations, the presence of hypoalbuminemia, hypogammaglobulinemia, and lymphopenia in affected siblings. These 10 patients with PIL were treated with high-protein, low-fat, medium-chain triglyceride oil-based diet, and fat-soluble vitamins. A repeat scan performed on 2 patients after treatment showed scintigraphic improvement (lower ^{99m}Tc-HSA uptake) of the protein loss (Figs. 1C and D) that was also evidenced clinically and biochemically. The cause of the enteric protein loss in the remaining 2 patients was the result of *Salmonella* colitis and giardiosis, as documented by a stool culture and a duodenal biopsy, respectively.

Table 2 summarizes the clinical features, biochemical data, and histological diagnoses of the remaining 6 children (3 boys, 3 girls; age range, 2–5 y; mean ± SD, 3.5 ± 1 y), who showed no abnormality on the ^{99m}Tc-HSA scans. All children had generalized edema and growth failure, 5 had diarrhea, and 2 presented with seizures. PIL was the clinical diagnosis in 5 patients (4 were confirmed pathologically), and the cause of protein loss could not be identified in 1 patient. All 6 cases were sporadic, with no other siblings diagnosed, despite the fact that first-degree consanguinity

TABLE 1
Clinical, Biochemical, and ^{99m}Tc-HSA Characteristics of 12 Children with PLE

Patient no.	Age (y)	Sex	Type	Clinical features	Alb/prot (mmol/L)	Early images*	Delayed images*	Diagnosis	Data
1	8	F	F (I)†	GE, GF, RCI	20/40	SB (2)	ND	PIL	Clinical, biochemical
2	10	F	F (I)†	GE, GF, D	18/35	ND	SB (2)	PIL	Clinical, biochemical
3	3	M	F (I)†	GE, GF, RSI	14/25	SB (3)	Colon (3)	PIL‡	Histological
4	6	M	F (II)†	GE, GF	17/30	Neg	Colon (3)	PIL	Clinical, biochemical
5	7	M	F (II)†	GE, GF, S	16/30	SB (2)	Colon (3)	PIL	Histological
6	14	M	F (III)	GE, S	17/35	SB (2)	Colon (3)	PIL	Clinical, biochemical
7	7	M	F (III)	GE, RSI	20/40	SB (2)	SB (3)	PIL‡	Clinical, biochemical
8	10	F	F (IV)†	GE, GF, D, RCI	17/28	SB (3)	Colon (3)	PIL	Clinical, biochemical
9	2	M	F (IV)†	GE, GF, D	18/29	SB (1)	Colon (3)	PIL	Histological
10	1	F	Sporadic†	GE, GF, D, RCI	19/29	SB (2)	Colon (3)	PIL	Histological
11	13	M	—	GE, D	15/30	SB (2)	Colon (3)	Giardiosis	Microbiological
12	8	M	—	GF, D	14/30	SB (3)	SB (3)	Enterocolitis (*Salmonella*)‡	Histological

*Intensity of uptake: 3 = marked uptake equal to the liver, 2 = moderate uptake less than the liver, 1 = mild uptake.
†Consanguinity, parents are first cousins. F = familial (roman numerals identify the 4 families).
‡Follow-up scan showed improvement.
Alb/prot = albumin/protein; GE = generalized edema; GF = growth failure; RCI = recurrent chest infection; SB = small bowel; ND = not done; D = diarrhea; RSI = recurrent skin infection; S = seizures.

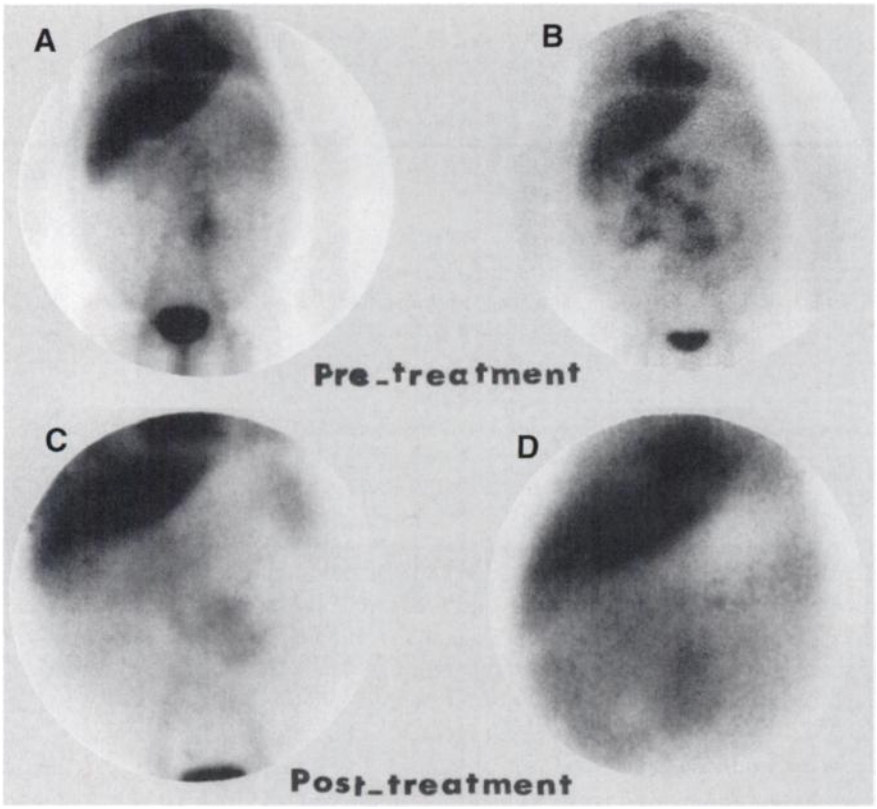

FIGURE 1. Patient 7: Anterior images of abdomen at 1 (A) and 4 h (B) after injection of ^{99m}Tc-HSA show excretion of radionuclide into small intestine, indicating probable site of protein loss. Anterior images of abdomen at 1 (C) and 4 h (D) in repeat study 2 mo after starting treatment show lower uptake in small intestine, indicating good therapeutic response.

was documented in 50% of the parents. Interestingly, 2 patients had infantile systemic hyalinosis (one associated with PIL and the other with unexplained PLE), manifested by painful joint contractures. The biochemical data showed a mean total protein level of 44 mmol/L (range, 35–55 mmol/L) and mean serum albumin level of 25.3 mmol/L (range, 22–32 mmol/L), which were significantly different from the first group (P = 0.0038 and P = 0.0008, respectively). Mean gammaglobulin level was 3.2 g/L (range, 2–6 g/L), mean corrected calcium level was 2 mmol/L (range, 1.8–2.6 mmol/L), and mean absolute lymphocyte count was 3826 (range, 1000–9100). These values were not significantly different from those of the first group (P = 0.8, P = 0.8, and P = 0.14, respectively).

DISCUSSION

Enteric ^{99m}Tc-HSA uptake was noted in 67% of the children, suggesting the site of protein loss. The location of the uptake was most likely in the small bowel in 91% of the early images and in 27% of the delayed images. Colonic activity was noted in 72% of the delayed images, most likely representing transit of activity rather than a second site of protein loss. The possibility of false-positive results caused by intestinal bleeding or free pertechnetate was excluded by the absence of melena and stomach uptake, respectively. Follow-up scans after treatment were obtained in 3 patients and showed less uptake, indicating improvement that was confirmed clinically and biochemically.

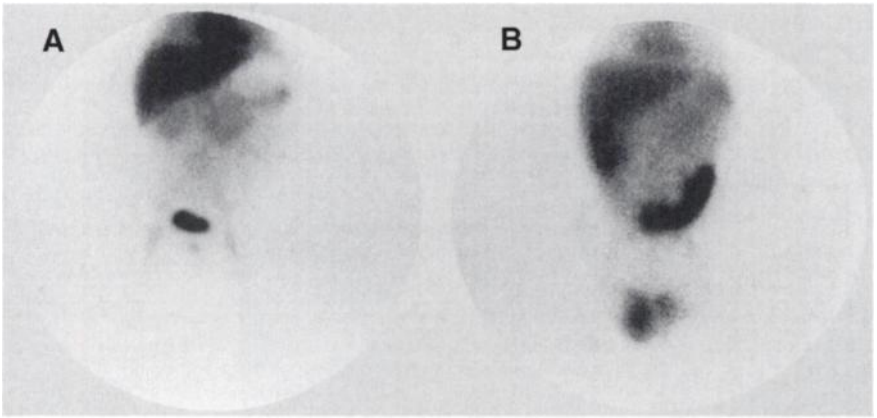

FIGURE 2. Patient 3: Anterior images of abdomen at 1 (A) and 20 h (B) after injection of ^{99m}Tc-HSA show excretion of radionuclide into small bowel and colon, respectively.

TABLE 2
Clinical and Biochemical Characteristics of 6 Children with PLE and Negative ^{99m}Tc-HSA Scans

Patient no.	Age (y)	Sex	Type	Clinical features	Alb/prot (mmol/L)	Diagnosis	Data
1	5	M	Sporadic	GE, GF, D	22/35	PIL	Histological
2	4	F	Sporadic	GE, GF, D	25/44	PIL	Histological
3	3	M	Sporadic*	GE, GF, S	22/40	PIL	Clinical, biochemical
4	4	F	Sporadic*	GE, GF, D, S	25/40	PIL	Histological
5	2	F	Sporadic*	GE, GF, D, PJC	26/55	PIL, infantile systemic hyalinosis	Histological
6	3	M	—	GE, GF, D, PJC	32/50	Unexplained PLE, infantile systemic hyalinosis	Clinical, biochemical

*Consanguinity; parents are first cousins.
Alb/prot = albumin/protein; GE = generalized edema; GF = growth failure; D = diarrhea; S = seizures; PJC = painful joint contractures.

PIL was the underlying cause of protein loss in 83% of patients. All of these children were clinically symptomatic, with generalized edema, growth failure, diarrhea, recurrent infection, and/or seizures. However, the ^{99m}Tc-HSA scan was positive in only 67% of these patients. These scan-positive patients had more severe hypoalbuminemia/hypoprotinemia and their mean age was significantly higher compared with the scan-negative patients. These findings presumably reflect a higher rate of protein loss that could be related to the disease progression. The negative-scan results are not unexpected, as the disease could be focal or mild as reflected by the biochemical findings.

PIL, consisting of wide villi, dilated lacteals, and enlarged submucosal lymphatics, may occur as an isolated abnormality or as a part of a more generalized syndrome with variable associated features and inheritance patterns (*14,15*). None of the children in this study had any of these associated congenital anomalies. However, 2 children had painful joint contractures, supporting the diagnosis of infantile systemic hyalinosis. Interestingly, first-degree consanguinity was documented in the parents of 11 children. Nine children in 4 families most likely had a familial form of the disease (*16*).

Other diagnostic tests of PLE include α-1-antitrypsin, fecal α-1-antitrypsin, and intestinal clearance of α-1-antitrypsin. These have been used as reliable screening tests for the presence of enteric protein loss and have also been shown to correlate with disease activity and response to therapy in children with various gastrointestinal disorders. Furthermore, α-1-antitrypsin clearance has been shown to correlate closely with determinations made by the intravenous $^{51}CrCl_3$ technique (*1*). However, because of the limitations of these procedures (*1*) and their unavailabilty in our institution, we have been using ^{99m}Tc-HSA scanning to document PLE scintigraphically. This has also been recommended as a screening test, and ^{99m}Tc-HSA is considered the tracer of choice for scanning patients with PLE (*5*). Our data suggest that the scan has a higher sensitivity in patients with lower albumin and total protein values, presumably reflecting a higher rate of protein loss. These findings are somewhat analogous to the detection of gastrointestinal blood loss using ^{99m}Tc-HSA or ^{99m}Tc-red blood cell scanning (*17*). Albumin challenge has been reported to increase the sensitivity of the scan in 1 patient (*12*). A high-fat meal during the evening before endoscopic evaluation may make the diagnosis more apparent (*18*). Recently, ^{99m}Tc-dextran (*19*) and ^{99m}Tc-human immunoglobulin (*20*) have been reported to show intestinal uptake in 2 patients with PLE.

A small number of cases of PLE detected by ^{99m}Tc-HSA have been reported in children (*10–12*). The underlying pathological conditions have included acute mesenteric lymphadenitis (*10*), primary oxalosis (*10*), Fontan operation (*11*), and infantile systemic hyalinosis (*12*). These secondary causes of enteric protein loss in addition to PIL should be considered in the interpretation of the ^{99m}Tc-HSA scan performed in a patient with PLE.

CONCLUSION

^{99m}Tc-HSA scanning is a useful test in establishing the diagnosis of PLE. It is likely to be positive in patients with lower albumin and total protein values, presumably reflecting a higher rate of protein loss.

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