Liver Scintigraphic Features Associated with Alcoholism

David E. Drum and Judith O. Beard

Harvard Medical School, Peter Bent Brigham Hospital, Children's Hospital
Medical Center and Sidney Farber Cancer Institute

The relationships between scintigraphic features and clinical alcoholism were studied by review of 2,406 liver scintiphotos. Two distinct patterns were significantly associated with alcoholism: (a) heterogeneous distribution of radiocolloid in the liver, and (b) jointly increased uptake of tracer by the spleen and vertebral bone marrow. A total of 13 overall patterns were found to distinguish, with considerable reliability, alcoholics from all other patients. This finding reflects the frequency with which alcohol abuse is associated with hepatic dysfunction in hospital patients.

These observations indicate an important role for the nuclear medicine physician in detection of alcoholism among patients referred for liver-spleen imaging, and they form a basis for comparison with the diagnostic efficacy of other methods of evaluating diffuse liver diseases.

Gamma imaging of the liver is an ancillary diagnostic examination frequently performed for general hospital patients. Although this method is most commonly applied in cancer detection, it is also ordered when liver enlargement, jaundice, ascites, or abnormal liver-function tests raise diagnostic questions (*1,2*).

Since hepatic abnormalities are the most common documented evidence for alcoholism in hospitalized patients (*3,4*), it would seem that some features of the liver scintiscan might be useful in the detection of alcoholism among patients referred for scanning in addition to, and regardless of, the primary focus of the referring physician's diagnostic efforts. Several reports have described scintigraphic changes associated with cirrhosis or other parenchymal liver diseases (*58*), but the scintiscan features were not related to behavioral alcohol abuse.

To be diagnostically useful, alterations of the liver image must be described in terms of their sensitivity and specificity for the disease causing the abnormalities in question. This report presents such data for scintigraphic features associated with clinical alcoholism in the ambulatory and admitted patients of an urban general hospital.

MATERIALS AND METHODS

Data base. Detailed reviews of the medical records and scintigraphic findings from all 2,406 examinations performed between 1970 and 1974 formed the basis for the analyses. Ten percent of these were repeated scans; all repeat examinations were made more than 1 mo after any prior study. Forty-seven percent of the livers were examined, within 2 mo of scintigraphy, by closed needle biopsy, surgical observation, surgical biopsy, or postmortem examination. Thus the histopathology underlying 1,133 of the liver scans was known with the degree of confidence permitted by these methods of observation. For 1,273 of the liver scintiphotos, only clinical and chemical evidence for the liver status was available. These studies were presumably performed for less ill or less complex patients, hence their patterns are considered separately. They constitute, nevertheless, an important group to consider because they may include patients at earlier stages of alcoholism.

At the time of the chart reviews, no less than 12 mo after each scan, 18% of the patients studied were judged alcoholic by the authors and one assistant, according to the criteria of the National Council on Alcoholism (NCA) (4,9). These very detailed NCA criteria may be condensed to define a person who drinks as alcoholic if there is evidence of one or more of the following: (a) withdrawal or tolerance phenomena; (b) consumption of a fifth of a gallon (757 cc) of whiskey, or its ethanol equivalent, for more than one day; (c) alcoholic hepatitis, Laennec's cirrhosis, or other major alcohol-associated illnesses; (d) drinking despite strong medical or social contraindications, or blatantly indiscriminate use of alcohol; (e) blood ethanol concentration over 3 g/l at any time, or over 1.5 g/l without symptoms; and (f) combinations of both behavioral and physical minor criteria—e.g., morning drinking plus otherwise unexplained evidence of liver abnormality. The nonalcoholics included all other patients referred for liver scintiscans, regardless of their diagnoses.

Hepatic scintigraphy. Hepatic scintiphotos were begun 10–30 min after i.v. injection of 3–5 mCi of Tc-99m sulfur colloid*. The particle-size distribution of these preparations has been reported (10). An Anger camera with a 25-cm diameter crystal and 140-keV diverging collimator was employed in all cases. Anterior views (630,000 counts), posteriors (630,000), and right laterals (540,000) were obtained for every patient. Two point sources 10 cm apart at the collimator face were photographed to aid estimation of organ size.

The gamma images were evaluated in the course of routine practice by the assigned one of five staff physicians board-certified in nuclear medicine. Their descriptions of the scintiscans, largely following a systematic approach applied here since 1970 (1),

were retrospectively examined for the following features: a) Focal defect(s): one or more clearly delimited areas of absent or minimal radiocolloid accumulation surrounded by normal density; b) Heterogeneity: irregular distribution of radiocolloid within the liver; c) Hepatomegaly: any liver image with a vertical height greater than 17 cm and a horizontal width greater than 18 cm (11); d) Extrahepatic changes: splenomegaly and/or increased uptake of radiocolloid by the spleen (greater density than the liver in the posterior view), bone marrow, or lungs.

Data analyses. Features of the hepatic scintiphotos were analyzed for sensitivity and specificity according to the following accuracy parameters: a) True-positive (TP) ratio: the fraction of scintiphotos from patients with evidence of alcoholism which exhibited abnormal features as specified; a measure of sensitivity; b) False-positive (FP) ratio: the fraction of scintiphotos from patients with no evidence of alcoholism which exhibited abnormal features as specified; a measure of nonspecificity.

RESULTS

Hepatic scintigraphic findings. Of the alcoholic patients for whom direct examination of the liver was made, only 27% showed no abnormality in the liver image—a significant difference from nonalcoholics (Table 1). Twenty-one percent of the alcoholic patients exhibited heterogeneity of radiocolloid distribution alone, and another 20% showed heterogeneity and hepatomegaly (p < .01). Focal defects, either alone or with other changes, were observed less commonly among alcoholics. Of the nonalcoholics for whom direct examination of the liver was available, 45% exhibited a fully normal liver scintiphoto, 17% exhibited focal defects alone, and only

TABLE 1. HEPATIC SCINTIGRAPHIC CHANGES ASSOCIATED WITH ALCOHOLISM

| | Percentage of each patient group | | | |
| | Livers directly examined | | No direct examination | |
Hepatic scintigraphic findings	Alcoholic (N = 184)	Nonalcoholic (N = 949)	Alcoholic (N = 251)	Nonalcoholic (N = 1022)
Normal	27*	45	45*	66
Focal defects	11†	17	2*	8
Heterogeneity of radiocolloid distribution	21*	10	19*	7
Focal and heterogeneous changes	3	3	1	2
Hepatomegaly only	9	8	12*	7
Hepatomegaly with focal defects	3	6	0	4
Hepatomegaly with heterogeneity	20*	9	18*	5
Hepatomegaly, focal defects and heterogeneity	5	3	4*	1

* p < 0.01.
† p < 0.05.

19% exhibited heterogeneity alone or in combination with an enlarged liver.

Among patients with only clinical data to compare with the scintigraphic diagnosis, a high percentage of both alcoholics and nonalcoholics—45 and 66%, respectively (p < .01)—exhibited normal liver images. Heterogeneity was again commonly noted in the alcoholics: in 18% as an isolated finding and in 19% associated with an enlarged liver. The corresponding percentages for the nonalcoholics were 7 and 5%, resulting in a significant difference (p < .01). Hepatomegaly alone or with heterogenity was a notable correlate of alcoholism (p < .01) for these less complex patients, as is consistent with clinical observations reported elsewhere (4,25).

Extrahepatic scintigraphic changes. These included splenomegaly, increased splenic uptake of radiocolloid relative to the liver, increased bone-marrow uptake of radiocolloid, focal defects in the spleen, and absent spleen either singly or in combination with other abnormalities (Table 2). Only two abnormal patterns—increased radiocolloid uptake by both bone marrow and spleen, with or without splenomegaly—occurred with significantly greater frequency both in alcoholics whose livers were directly examined and in those without such studies (p < .01). Increased splenic uptake of radiocolloid alone occurred more often in the nonalcoholics, but the difference was not significant. Extrahepatic deposition of radiocolloid was abnormal more often in alcoholic patients than in nonalcoholics (p < .01).

Among patients with livers not directly examined neither the occurrence of increased splenic uptake of radiocolloid nor the combined features of splenomegaly and increased splenic uptake were significantly different when alcoholics and nonalcoholics were compared.

Combined liver-spleen scintigraphic findings. Typical practice in nuclear medicine involves description and interpretation of *all* information in a scintiphoto. In order to decide which of 56 combined patterns are diagnostically useful—i.e., which group of features occurs more often in alcoholics—we computed the ratio of the *observed* to the *expected* occurrence of each scintigraphic pattern for all alcoholics against all patients examined, based on the measured alcoholism prevalence of 18% (Table 3). Each cell of the matrix shows this numerical ratio; values increasingly different from 1.0 indicate useful patterns. The data were analyzed by the chi-square technique, and those numbers indicated by double daggers indicate overall *scintiphoto patterns* that were significantly (p < .05) associated with *clinical alcoholism*. Certain patterns were observed in five or less alcoholic patients; these are indicated by single daggers, and their numerical values cannot be considered reliable. One scintiphoto pattern was *less* often seen in alcoholics than in nonalcoholics. This was the pattern of focal hepatic defect(s) only, occurring with an observed-to-expected ratio of 0.42.

To illustrate the computations of Table 3, consider the abnormal pattern most commonly seen in the scintiscans of alcoholics: heterogeneous or poor liver uptake of radiocolloid with increased splenic and bone-marrow uptake. This was observed in 73 of the total of 2,406 scintiphotos. Since 18% of all patients were alcoholics, the expected number of alcoholics showing this pattern would be 0.18 × 73 = 13. In fact, 35 of the alcoholics exhibited the pattern, for an observed-to-expected ratio of 35/13

TABLE 2. EXTRAHEPATIC SCINTIGRAPHIC CHANGES ASSOCIATED WITH ALCOHOLISM

| | Percentage of each patient group | | | |
| | Livers directly examined | | No direct examination | |
Extrahepatic scintigraphic findings	Alcoholic (N = 184)	Nonalcoholic (N = 949)	Alcoholic (N = 251)	Nonalcoholic (N = 1022)
Splenomegaly	4	6	2	5
Increased splenic uptake of radiocolloid	5	9	6	6
Splenomegaly and increased splenic uptake	8†	4	2	3
Increased radiocolloid uptake by bone marrow	6	5	7	4
Increased radiocolloid uptake by bone marrow and spleen	25*	10	25*	8
Increased radiocolloid uptake by bone marrow and spleen with splenomegaly	11*	4	8*	2
Focal spleen defects with increased bone-marrow uptake	0	1	0	0
Focal spleen defects, normal marrow uptake	1	2	0	1
Spleen absent	4	3	0	2
No extrahepatic changes	36*	55	51*	69

* p < 0.01.
† p < 0.05.

TABLE 3. RATIOS OF OBSERVED TO EXPECTED SCINTIGRAPHIC PATTERNS: ALCOHOLICS AGAINST ALL PATIENTS*

Hepatic patterns	Extrahepatic radiocolloid patterns						
	No extra-hepatic changes	Spleno-megaly	Increased splenic uptake	Spleno-megaly and increased splenic uptake	Increased bone-marrow uptake	Increased splenic and marrow uptake	Spleno-megaly and increased splenic and marrow uptake
Normal liver and spleen	0.86	—	—	—	—	—	—
Normal liver only	—	0.13†	0.65†	0.42†	1.0	1.2	0.9†
Focal hepatic defects only	0.42‡	0.9†	0†	0†	1.5	1.1†	1.4†
Heterogeneous or poor liver uptake	1.3	1.1†	0.51†	3.1‡	1.8‡	2.7‡	2.7‡
Focal and heterogeneous changes	0†	0†	0†	0†	1.6†	2.1‡	1.1
Hepatomegaly only	1.3	1.3	1.7†	1.2†	2.8†	2.2‡	1.1†
Hepatomegaly plus focal defects	0.33†	0†	0.12†	0†	0†	0.70†	3.7†
Hepatomegaly plus heterogeneity	2.1‡	0.40†	2.1‡	2.1‡	3.7‡	2.6‡	1.9‡
Hepatomegaly plus heterogeneity and focal defects	1.8†	0†	0.9†	1.6†	0†	3.0‡	2.8†

* Excluding scans with focal splenic defects or asplenia.
† Less than 5 alcoholics with the indicated pattern.
‡ $p < 0.05$.

= 2.7. For these numbers, chi-square = 45, indicating that the pattern distinguished alcoholics from nonalcoholics with better than 99% confidence.

As expected from Tables 1 and 2, heterogeneous uptake of radiocolloid was a significant indicator of alcoholism when associated with the four extrahepatic patterns noted. On the other hand, heterogeneity without extrahepatic changes, or with splenomegaly alone, or with increased splenic uptake alone, was *not* significantly diagnostic. The combination of focal and heterogeneous changes was sufficiently uncommon that it was a useful diagnostic correlate only when accompanied by excessive spleen and marrow uptake. Similarly, hepatomegaly without heterogeneity was a correlate of alcoholism only when observed with increased spleen and bone-marrow uptake. The combination of hepatomegaly and heterogeneity was a very common pattern in alcoholics, either alone, or associated with increased splenic uptake or increased spleen and marrow uptake, with or without splenomegaly. These ratios thus identify the 13 liver-spleen patterns that were associated, at a 95% or better confidence level, with the clinical diagnosis of alcoholism.

Diagnostic accuracy of scintigraphy. From these data, accuracy parameters were calculated for scintiscan features as diagnostic clues to clinical alcoholism (Table 4). Among patients who later had direct examination of the liver, 49% of those who were alcoholic exhibited heterogeneity in the liver image. For the patients not so examined, 43% of those with alcoholism exhibited heterogeneous distribution of radiocolloid. The false-positive ratios were 0.25 and 0.15, respectively.

A similar analysis for increased bone-marrow uptake of radiocolloid, occurring in any pattern, revealed that 40% of all alcoholics showed this feature on their scintiscans.

The results of disjoining these two distinct pattern variables (that is, computing accuracy parameters based on making the diagnosis of clinical alcoholism with either or both variables abnormal) showed a sensitivity of 59% in patients with direct liver examination. For the patients with proven liver disease, the increase in true-positive and false-positive ratios was quite large. The accuracy parameters for the patients studied by clinical evidence alone increased to a TP ratio of 0.54 and a FP ratio of 0.20.

Indications for scintigraphy. The indications cited by referring physicians for examination by the liver-spleen scan were quite different for the alcoholic and nonalcoholic patients (Table 5). For example, 33% of the alcoholics were referred with a question of metastases, 21% were sent for evaluation of known parenchymal liver disease, and 29% were referred because of puzzling clinical findings (e.g., abnormal liver-function tests, hepatomegaly, epigastric mass, or jaundice). Of the nonalcoholics, 62% were referred with either known or suspected metastases, only 3% with known parenchymal disease, and 20% with abnormal clinical findings.

Distribution of hepatic diseases. The final liver-

TABLE 4. DIAGNOSTIC ACCURACY OF LIVER SCINTIGRAPHY FOR DETECTION OF ALCOHOLISM

Test pattern	Patients with direct liver examination (N = 1133)		Patients without direct liver examination (N = 1273)	
	TP* ratio	FP* ratio	TP ratio	FP ratio
1. Heterogeneity	0.49	0.25	0.43	0.15
2. Bone marrow uptake	0.41	0.21	0.40	0.14
3. Heterogeneity or bone marrow uptake, or both	0.59	0.35	0.54	0.20

* TP = true-positive; FP = false-positive.

related diagnoses assigned these patients differed importantly from the indications that led to scinti-scanning (Table 6). Although 33% of the alcoholics with documented liver disease were examined for metastases, only 10% in fact proved to have such disease. Among alcoholics without direct examina-tion of the liver, this discrepancy was even more marked (35% against 2%). Similarly, 62% of non-alcoholics were referred in search of metastases; only 26% proved to have metastases and 30% had un-derlying parenchymal liver disease unrelated to al-coholism. Jointly, these numbers (Tables 5 and 6) show that the diffuse parenchymal liver diseases are the most common hepatic abnormality in patients referred for imaging in this institution even though evaluation for metastases is the most common indi-cation for referral.

DISCUSSION

The liver-spleen scintiphoto is never pathogno-monic, but it may alert the primary physician to the presence of certain diseases not otherwise considered, or may warn him to confirm clinical suspicions of the presence or absence of disease. For example, an increase in the ratio of image intensity over the spleen to that over the liver has been cited as indica-tive of cirrhosis (7,8,12–14). The data here define the contribution that hepatic scintigraphy affords to detection of *clinical* alcoholism—a common illness

TABLE 5. INDICATIONS FOR HEPATIC SCINTISCANNING

Indication for scintigraphy	Percentage in each indication group			
	Livers directly examined		No direct examination	
	Alcoholic (N = 184)	Nonalcoholic (N = 949)	Alcoholic (N = 251)	Nonalcoholic (N = 1022)
Search for metastases	33	62	35	62
Clinical abnormalities (hepatomegaly, jaundice, mass, or abnormal liver-function tests)	29	19	32	22
Evaluation of parenchymal disease	21	3	25	3
Search for abscess	9	8	5	6
Hematologic disorders	6	7	2	5
All other	2	4	1	2

TABLE 6. MAJOR HEPATIC DISEASES OF PATIENTS REFERRED FOR SCINTIPHOTOS

Final diagnosis	Percentage in each disease group			
	Livers directly examined		No direct examination	
	Alcoholic (N = 184)	Nonalcoholic (N = 949)	Alcoholic (N = 251)	Nonalcoholic (N = 1022)
Diffuse parenchymal disease				
1. Cirrhosis	34	6	19	1
2. Fatty infiltration	17	9	34	3
3. Portal disease	15	10	2	3
4. Hepatitis	7	5	10	8
Subtotal	73	30	65	15
Metastases	10	26	2	10
All other diseases	4	15	2	11
No disease	13	29	31	64

among general hospital patients—which may cause several distinctive kinds of liver disease (*15*) and which is frequently overlooked by clinicians (*4,16–18*).

Among hospitalized patients the most common objective manifestations of alcoholism are abnormal liver-function tests (*4*). Such findings are neither specific for the liver itself nor for the types of liver disease (*19,20*), and it is difficult to correlate histologic severity with the degree of chemical-function-test abnormality for fatty liver or cirrhosis (*21–24*). The figures reported here suggest that the scintiscan reflects rather accurately (albeit etiologically nonspecifically) the presence of diffuse liver disease in both alcoholics and nonalcoholics. This circumstance is clinically useful in the population studied because alcohol abuse is by far the single most common cause of liver disease at our institution, and, presumably, at similar general hospitals. Even in more selected populations, such as those of cancer-treatment centers, the diffuse liver diseases, including those due to alcohol abuse, cannot be neglected because their effects on liver-function tests and CEA values may complicate decisions as to management.

Nuclear medicine physicians may use the patterns identified by this study to facilitate awareness of patients worthy of further evaluation in regard to alcohol abuse. Approximately 80% of patients with actual alcoholic liver disease (59% of all alcoholics referred for scans) could be detected with only the simple composite test proposed in Table 4. Even more alcoholics might be identified by application of the patterns delineated in Table 3.

This capability assumes added significance both (a) because alcoholism is so often overlooked, and (b) in light of the discrepancy between the diseases actually present and the indications for which the scans were ordered. Independent of whether their livers became subject to direct examination, about one-third of the alcoholics and two-thirds of the nonalcoholics were referred in search of metastases. However, only 10% of the alcoholics actually had metastases, and 26% of the nonalcoholics were proven to have metastases when their livers were directly examined. Both groups more often had parenchymal liver disease, a fact that should be recognized by referring clinicians and by those interpreting scintiphotos. Moreover, for these diseases the implications of FP classification are minimal (e.g., further questioning), unlike the consequences for the patient judged to have hepatic metastases.

Such projections of scintigraphic findings into clinical diagnosis and management are highly dependent upon accurate description and interpretation of the scan image. Although an "increased spleen-to-liver ratio" has been called a reliable indicator of cirrhosis (*5–8*), it was not uniquely associated with *alcoholism* in this study, even though the alcoholics included a large fraction of patients with cirrhosis (34% of those with direct proof of liver disease). It is possible that differences in patient sampling and in imaging technique (i.e., use by others of the rectilinear scanner and densitometric measurements) account for this discrepancy. Our observations were made by methods that closely reflect clinical practice with the gamma camera, and they should not be projected to other methodologic approaches, such as studies employing a "grading" of heterogeneity or of bone-marrow uptake (*8*).

Moreover, there may be in use colloid preparations that would exhibit extrahepatic distributions quite different from those reported here. It is probable that the physicochemical properties of any radiocolloid preparation critically affect its extrahepatic deposition. Thus, radiopharmaceutical uniformity must be maintained if the full potential of information available from radiocolloid imaging is to be realized.

Although we segregated our data according to whether or not the livers were directly examined, the relationships between individual scan features of the alcoholic and the nonalcoholic differed little. In general, our findings were independent of whether the livers were directly examined or not, thereby still further enhancing their usefulness in less complex patients with presumably earlier stages of alcoholism. The proportion of normal scintiphotos was higher for both alcoholics and nonalcoholics whose course did not lead to direct liver examination, even though the indications for radionuclide imaging were not different.

In addition to the importance of liver heterogeneity and increased radiocolloid uptake by the bone marrow, other observations were notable. In patients with histologic or surgical examination of the liver, hepatomegaly by our criteria (*10*) was not a useful indication of alcoholism as opposed to the other diseases. Hepatomegaly was significant only in those presumably less ill patients (whose livers were not directly examined), in accord with clinical findings reported elsewhere (*25*). For the entire group of patients, hepatomegaly was a useful clue to alcoholism only in combination with increased spleen and marrow uptake of tracer and/or with heterogeneity. Similarly, focal defects were not indicative of alcoholism unless occurring in combination with both hepatomegaly and increased spleen and marrow uptake.

These observations and those tabulated elsewhere in this paper represent an overview of the interpretive and descriptive capabilities of scintigraphy for

evaluating the liver diseases of alcoholism during a technically homogeneous period of development in the field. Additional refinements, and perhaps accuracy, may be expected to result from routine quantitative studies of time-dependent changes in radiocolloid distribution after injection (26–28) and from computer-based measurement and interpretation of the image features described in this work. The observations reported here should provide a basis for comparison of the diagnostic efficacy of the radiocolloid scintiphoto with alternative methods for hepatic imaging of patients with diffuse liver disease.

How is the information reported here best applied in the practice of nuclear medicine? The referring physician should always be informed unequivocally that alcoholism is a possible cause of the abnormal scintiphoto patterns noted above. His responsibility then is to pursue a definite diagnosis, or exclusion thereof, by questioning aimed at documenting the behavioral abnormalities characteristic of the disease (9).

FOOTNOTE

ACKNOWLEDGMENTS

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