Outcome of Hepatobiliary Scanning in Neonatal Hepatitis Syndrome

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To evaluate the diagnostic information gained from hepatobiliary scanning in infants, we reviewed 86 consecutive infants who were ≤4 mo old and were treated for conjugated hyperbilirubinemia at the Hospital for Sick Children in Toronto between 1985 and 1993 and who had technetium iminodiacetic hepatobiliary scanning and a percutaneous liver biopsy performed in close temporal proximity. **Methods:** Retrospective reviews of hospital charts and blinded reviews of hepatobiliary scans were performed. **Results:** There were 58 male and 28 female infants (age range, 2–124 days; mean = 65 days). Hepatobiliary scanning failed to show biliary excretion into the gastrointestinal tract in 53 of 86 patients. Forty of these 53 had extrahepatic biliary atresia. The remaining 33 patients demonstrated biliary excretion into the gastrointestinal tract; 24 of 33 had neonatal hepatitis. Among 13 of the 53 patients who had no evidence of biliary excretion and who also did not have extrahepatic biliary atresia, 8 had idiopathic neonatal hepatitis, 4 had interlobular bile duct paucity and 1 had total parenteral nutrition-associated cholestasis. In this large series, no patient with extrahepatic biliary atresia showed bile drainage on hepatobiliary scanning. Fifty percent of patients with interlobular bile duct paucity but no extrahepatic obstruction failed to show biliary excretion of radionuclide. Twenty-five percent of patients (8 of 32) with idiopathic neonatal hepatitis demonstrated no biliary excretion. Hepatocellular extraction was examined by semiquantitative analysis in the nondraining, nonbiliary atresia patients (12 of 53). Four of these 12 patients demonstrated poor liver extraction. Three patients had idiopathic neonatal hepatitis, and one had bile duct paucity. Therefore, four of eight neonatal hepatitis patients had normal extraction, suggesting that poor versus good liver hepatocyte clearance cannot accurately identify neonatal hepatitis. **Conclusion:** Hepatobiliary scanning requires cautious interpretation. Nondraining scans may indicate severe neonatal hepatitis or the presence of interlobular bile duct paucity.

Key Words: hepatobiliary scan; technetium-99m-DISIDA; neonatal hepatitis syndrome; extrahepatic biliary atresia

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Many different disease processes can present clinically as hepatic dysfunction with conjugated hyperbilirubinemia in the first 3 mo of life. These are grouped as the neonatal hepatitis syndrome. It is imperative to identify surgically correctable lesions, that is, to distinguish extrahepatic biliary obstruction from neonatal hepatitis. Hepatobiliary scintigraphy has proven useful in these investigations because demonstrating the passage of radiotracer into the intestinal tract indicates an intact extrahepatic biliary system (*1–5*). Previously, the ^{131}I-rose bengal fecal excretion procedure was used to differentiate extrahepatic biliary atresia from neonatal hepatitis but with only moderate success, mainly due to difficulties in collecting samples properly. The advent of technetium-labeled iminodiacetic acid (IDA) compounds has improved our ability to differentiate these two disease groups. Although some claim a specificity of 100% for hepatobiliary scans in extrahepatic biliary atresia (*6*), most find a lower specificity (*7*).

We have noted in selected cases that hepatobiliary scintigraphy may fail to show drainage in several other neonatal liver diseases, not only in severe idiopathic neonatal hepatitis but also in conditions characterized by interlobular bile duct paucity. We also found that hepatocellular extraction of radiotracer was not an accurate discriminator between neonatal hepatitis and other cholestatic conditions. The aim of our study was to test these observations by reviewing hepatobiliary scans in a very large number of patients representing a broad spectrum of neonatal hepatobiliary disease. We therefore analyzed records and scans of all neonates with conjugated hyperbilirubinemia who had both a hepatobiliary scan and a percutaneous liver biopsy during the period 1985–1993 at the Hospital for Sick Children in Toronto.

MATERIALS AND METHODS

One hundred eighty-one patients with conjugated hyperbilirubinemia underwent hepatobiliary scanning between January 1985 and April 1993. Eighty-six of these met our inclusion criteria: age under 4 mo, documented conjugated hyperbilirubinemia and diagnostic procedures including percutaneous liver biopsy in temporal proximity to scanning.

Before hepatobiliary scanning, all patients received phenobarbital (5 mg/kg/day) in two divided doses by mouth for 3–5 days before the scan. Patients were not fed for 1 hr before and 2 hr after the injection of technetium-labeled scanning agent. Anterior images of the abdomen were obtained at 5-min intervals up to 1 hr after injection. Thereafter, images were obtained at 2, 4, 6 and 24 hr postinjection. All scans were evaluated by two radiologists independently and without prior knowledge of the patient's diagnosis. A negative or "nondraining" scan was defined as one showing no excretion of radiolabeled tracer into the small intestine 24 hr after injection. A positive or "draining" scan disclosed radiolabeled isotope in the small intestine at some time during the 24-hr period after injection. Nondraining scans of patients without biliary atresia were evaluated to assess liver extraction. Poor extraction was defined as decreased liver activity and persistence of cardiac blood-pool activity over 60 min. Good extraction demonstrated prompt diffuse liver activity on the initial images, with no cardiac blood-pool activity visualized by 5 min.

The diagnosis of neonatal hepatitis was based on the liver biopsy finding of giant cell transformation, hepatic parenchymal inflammation, focal necrosis or ballooning degeneration of hepatocytes. This diagnosis was supported by clinical history and specific investigations, including protease inhibitor (PI) typing for alpha-1-antitrypsin deficiency, metabolic studies, bacterial and viral cultures and serological studies for various viral infections. Idiopathic neonatal hepatitis was diagnosed when these etiologies were

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TABLE 1
Age of Patients Studied by Disease Category

	Range (d)	Mean (d)	Median (d)
Extrahepatic biliary atresia	16–124	65.2	70
Nondraining neonatal hepatitis	27–69	47	48
Draining neonatal hepatitis	31–111	57	71
Nondraining interlobular duct paucity	2–124	51	63
Draining interlobular bile duct paucity	34–124	86	79

excluded. Interlobular bile duct paucity was defined as major reduction in number or complete absence of intrahepatic bile ducts in portal tracts in an adequate liver biopsy specimen. Extrahepatic biliary atresia was diagnosed on the basis of liver biopsy histology consistent with large bile duct obstruction and the presence of an atretic extrahepatic biliary system at laparotomy.

RESULTS

The age range of the patients studied was 2–124 days, with a mean age of 65 days (approximately 9 wk). The age of patients by diagnostic category is shown in Table 1.

Of the 86 patients studied, 53 had nondraining hepatobiliary scans (Table 2). Of these 53 patients, 40 (75%) had extrahepatic biliary atresia. A typical scan is shown in Figure 1. The other 13 patients with nondraining scans included 8 with idiopathic neonatal hepatitis (15%), 4 with interlobular bile duct paucity and 1 with total parenteral nutrition (TPN)-associated cholestasis. Thirty-three patients had draining scans, and the diagnosis in the majority of these patients (24 of 33; 75%) was neonatal hepatitis. Two of these patients had alpha-1-antitrypsin deficiency, which was the cause of the neonatal hepatitis. Four patients with draining scans had interlobular bile duct paucity. The remaining five patients had various conditions, including four with multifactorial cholestasis of prematurity and one with nonspecific findings including hemosiderosis.

No patient with extrahepatic biliary atresia had a draining hepatobiliary scan. However, 25% of patients with neonatal hepatitis had nondraining scans. Interlobular duct paucity was associated with a nondraining scan in 50% of cases. TPN cholestasis was sufficiently severe to lead to a negative scan in one infant.

Twelve nondraining scans from patients without biliary atresia were assessed for extraction (Table 3). Eight of the 12 patients examined, including 4 with neonatal hepatitis, 3 with bile duct paucity and 1 with TPN cholestasis, demonstrated good liver extraction and prompt blood-pool clearance by 5 min (Fig. 2). Three patients with neonatal hepatitis and one with bile duct paucity demonstrated poor extraction of radiotracer.

Differences in age of patients did not appear to influence results in most disease categories. Infants with extrahepatic biliary atresia were approximately the same age as infants with neonatal hepatitis and positive scans. Infants with neonatal hepatitis with nondraining scans were slightly younger. Although infants with intrahepatic duct paucity and nondraining scans were significantly ($p < 0.01$, by chi-square analysis) younger than infants with duct paucity and draining scans; infants with duct paucity and negative scans were similar in age to infants with extrahepatic biliary atresia.

TABLE 2
Positive (Draining) and Negative (Nondraining) Hepatobiliary Scans by Disease Category in 86 Consecutive Patients

	Draining	Nondraining	Total
Extrahepatic biliary atresia	0	40 (100%)*	40
Neonatal hepatitis	24	8 (25%)	32
Interlobular duct paucity	4	4 (50%)	8
Miscellaneous	5	1 (17%)	6
Total	33	53 (62%)	86

*Numbers in parentheses indicate percent of total number.

TABLE 3
Hepatic Parenchymal Extraction of Tracer on Hepatobiliary Scanning in Nondraining Scans of Patients without Extrahepatic Biliary Atresia

	Extraction		
	Normal	Poor	Total
Neonatal hepatitis	4	3	7
Alagille syndrome	3	1	4
TPN cholestasis	1	0	1
Total	8	4	12

DISCUSSION

Hepatobiliary scans provide important information in the diagnosis of neonatal liver disease causing conjugated hyperbilirubinemia. However, because hepatobiliary scans are physiological studies, all that can be concluded from a nondraining scan is that the liver is unable to excrete the radiotracer. This may be a consequence of severe hepatocellular dysfunction, defective interlobular bile ducts or damage to medium-sized or large (extrahepatic) bile ducts. A nondraining scan may thus reflect several different hepatic diseases, not just extrahepatic biliary atresia. In this series of 86 infants, we found that only 75% of the nondraining scans occurred in patients with extrahepatic biliary atresia. This specificity is considerably lower than the 85%–100% that some claim (*8*).

We found that 25% of patients with neonatal hepatitis had nondraining scans. This is much higher than the 15% previously quoted in the literature (*3*). It is also higher than the incidence of severe cholestasis found by detection of bile in duodenal contents. Approximately one-half of these patients had the qualitative descriptor of "severe neonatal hepatitis" in the description of histopathology on liver biopsy. Differences in our findings compared to previous studies did not appear to find an age bias because patients had a similar range of ages and mean age at time of study as in previous smaller series (*2,3*). In particular, the age range of patients with extrahepatic biliary atresia was wide (2–17 wk).

Interlobular bile duct paucity may be associated with severe cholestasis. Almost one-third of patients with negative scans but not extrahepatic biliary atresia (4 of 13) had the diagnosis of bile duct paucity. Others have also reported nondraining hepatobiliary scans in Alagille syndrome (*4,5,9*). Our data reveal that 50% of our patients with duct paucity nevertheless had draining hepatobiliary scans, a proportion that has been reported elsewhere. However, in our series, these patients with draining scans were older than the infants with duct paucity and nondraining scans. These older infants may have recovered from severe cholestasis to some degree, although they presented at a later age with liver disease. The differentiation of intrahepatic duct paucity from extrahepatic biliary atresia is important because the Kasai portoenterostomy is generally not indicated for patients with intrahepatic duct paucity and may actually worsen their condition, making liver transplantation inevitable.

The presumption that hepatocellular extraction of radiotracer provides an additional sensitive and specific marker to discriminate between neonatal hepatitis and biliary atresia was not

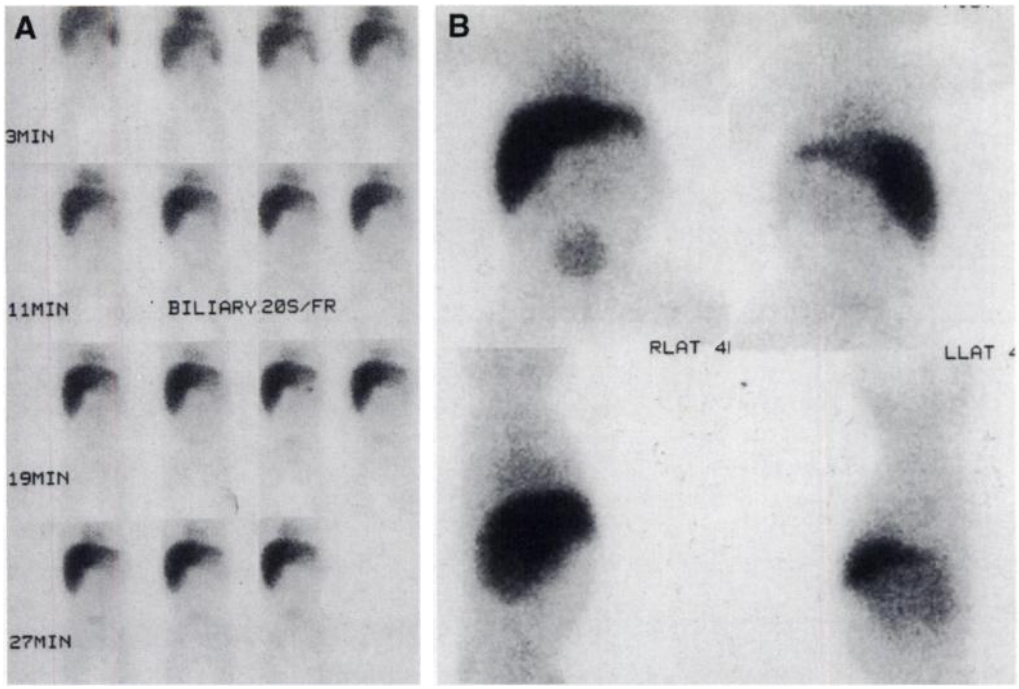

FIGURE 1. Nondraining hepatobiliary scan in extrahepatic biliary atresia. (A) Sequential images in the first 30 min showing good extraction of tracer. (B) Anterior and lateral images at 4 and 24 hr failed to show tracer in the intestinal tract.

confirmed in our series. Sixty-three percent (five of eight) of nondraining neonatal hepatitis patients had excellent extraction. Of the four patients with poor extraction, only three had neonatal hepatitis and one had bile duct paucity.

In this series, hepatobiliary scanning had a sensitivity of 100% for extrahepatic biliary atresia. By comparison, one biopsy was classified as "neonatal hepatitis" in an infant who proved to have extrahepatic biliary atresia at laparotomy (sensitivity of liver biopsy, 98%). A draining hepatobiliary scan provided strong evidence against the presence of extrahepatic biliary atresia. The existence of the entity "biliary atresia in evolution" is not supported by the data in this series, although studies were not designed to address this question directly. However, since accessioning to this study was closed, we have reviewed one child who had a draining hepatobiliary scan at 3 wk of age but was found at 3 mo of age to have extrahepatic biliary atresia. The specificity of hepatobiliary scanning in patients with neonatal cholestatic disease was only 74%. Percutaneous liver biopsy provided important information regarding the nature of the neonatal liver disease in these patients.

In summary, in this large series of patients, a nondraining hepatobiliary scan was not due to extrahepatic biliary atresia in more than one-quarter of patients. In these patients, other causes of poor biliary excretion, notably, severe neonatal hepatitis, interlobular bile duct paucity and choledocholithiasis, must be considered. In addition, our findings suggest that poor liver extraction is not specific for neonatal hepatitis, and good liver extraction does not exclude neonatal hepatitis. Percutaneous liver biopsy may provide valuable information regarding these diagnoses.

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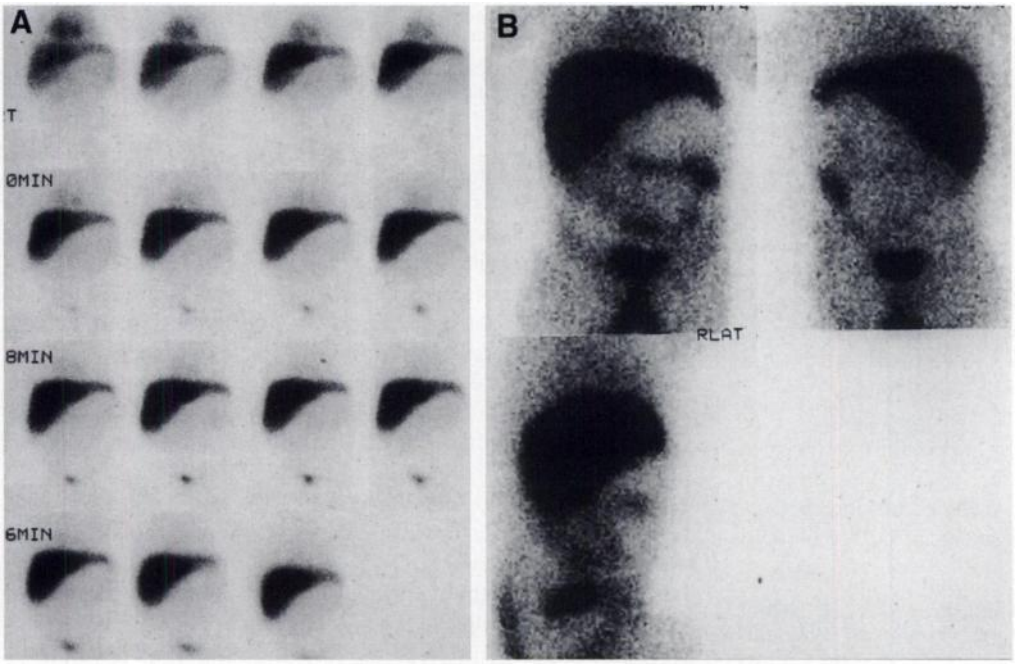

FIGURE 2. Hepatobiliary scan in clinically severe idiopathic neonatal hepatitis. (A) Sequential images in the first 30 min showing excellent extraction of tracer. (B) Anterior and lateral images at 5 hr showing tracer in the intestinal tract.

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The Rim Sign in Hepatic Abscess: Case Report and Review of the Literature

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We studied a previously healthy patient who presented with a 3-wk history of fever, flu-like symptoms and abdominal pain. **Methods:** Blood cultures were positive for *Escherichia coli*. A computed tomography (CT) scan revealed a 2-cm low-density focus in the right hepatic lobe. A technetium-99m-mebrofenin scan showed a photopenic area in the right hepatic lobe surrounded by a rim of activity greater than the adjacent parenchymal activity. **Results:** Gallbladder visualization was normal and the diagnosis of hepatic abscess was made. CT-guided percutaneous drainage of the lesion yielded six cc of pus, the culture of which grew *E. coli*, *Prevotella* and *Bacteroides fragilis*. Drainage and a 6-wk course of intravenous antibiotics were followed by clinical improvement and resolution of the abscess by CT. **Conclusion:** The rim sign and its possible mechanism of causation in hepatic abscess are discussed in this report, together with a review of the literature.

Key Words: rim sign; hepatobiliary scan; hepatic abscess

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Technetium-99m-labeled iminodiacetic analogs play a clinically important role in the diagnosis of a variety of hepatobiliary disorders. The analogs share the same hepatocyte uptake, transport and excretion pathways as bilirubin. Increased pericholecystic activity due to the inflammation associated with acute cholecystitis is a finding known as the rim sign. Here we present a case of an anaerobic hepatic abscess that ^{99m}Tc-mebrofenin scan demonstrated as a cold region surrounded by a rim of increased activity.

CASE REPORT

A 47-yr-old Caucasian male without a significant past medical history presented with a 3-wk history of fever, chills, night sweats, severe anorexia and malaise. Physical examination at admission revealed no focal abnormalities. The patient's temperature was 38°C, and his pulse was 123 bpm. The white blood cell level was increased at 19,900/mm^3. The patient's initial blood cultures at admission reported *Escherichia coli*.

A computed tomography (CT) scan with contrast revealed a 2-cm low-density abnormality within the right hepatic lobe (Figs. 1 and 2). The differential at the time included hepatic abscess or hemangioma, the latter of which was excluded by red blood cell scan. A ^{99m}Tc-mebrofenin scan was performed to rule out acalculous cholecystitis. Technetium-99m-mebrofenin (185 MBq) was injected intravenously. Imaging was performed using a large field-of-view gamma camera equipped with a low-energy all-purpose collimator. This study showed a photopenic area in the right hepatic lobe surrounded by a rim of activity greater than that of the adjacent parenchyma (Fig. 3). The gallbladder filled normally, thus essentially eliminating the diagnosis of acute cholecystitis.

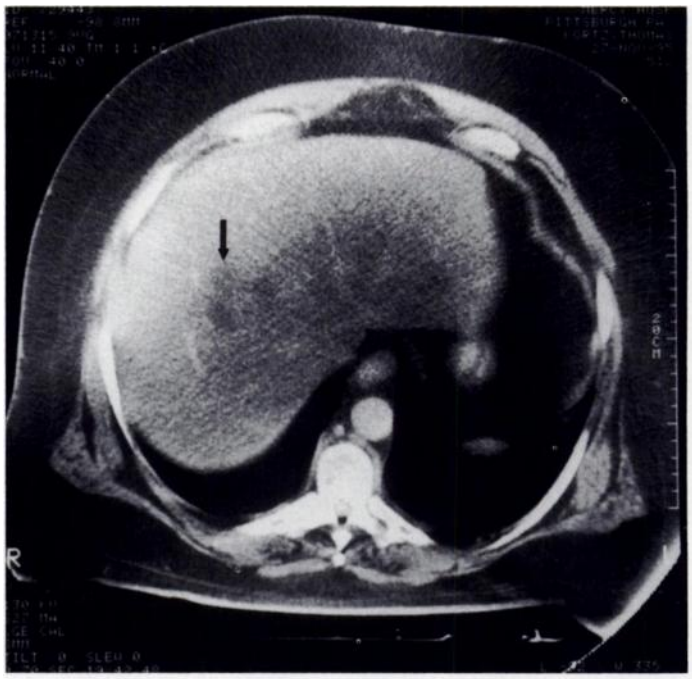

FIGURE 1. The initial contrast-enhanced CT showed a subtle low-density lesion in the right-middle hepatic lobe consistent with early hepatic abscess.

CT-guided percutaneous drainage of the liver abscess was performed on two occasions after the ^{99m}Tc-mebrofenin scan. Cultures grew *E. coli*, *Prevotella* and *Bacteroides fragilis*. The patient was given a 6-wk course of intravenous ampicillin and sulbactam. The hepatic abscess was followed by CT and noted to resolve. Three months after the initial presentation, the patient was readmitted with complaints of abdominal pain and diarrhea. Biopsy of the large bowel disclosed the diagnosis of ulcerative colitis.

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